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THE TREATMENT OF EPILEPSY AND OF MIGRAINE*

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THE treatment of epilepsy and of migraine is a large subject, both in extent and in difficulty. It concerns general practitioners as well as workers in laboratories.

In the United States, assuming there are 100,000 practicing physicians, the average physician should have the care of about five persons with epilepsy and fifty with migraine. The great majority of these persons are not patients, owing in part to the fact that physicians give little interest and less encouragement to would-be patients. A seizure of headache or of a convulsion is looked on as an act of God, against which the medical profession is helpless. This fatalistic attitude born of thousands of years of experience is no longer necessary. Cure is still a word to be used with caution, but some measure of relief is almost always possible.

First, let us examine the linkage of these two disorders, which at first thought are alike only because both occur in attacks, the person in the free intervals being essentially normal. In many respects the two conditions are opposites. Socially, migraine and epilepsy are far apart. Migraine appears oftener in the professional, brain-using group and epilepsy in the laboring group. Migraine is respectable, even fashionable; epilepsy is an outcast in society, a Cinderella of medicine. Epilepsy is divided equally between the sexes; migraine is twice as common in women as in men. Epilepsy develops most frequently in infancy and adolescence, migraine in adolescence and beyond. Epilepsy often leads to mental deterioration; migraine does not. Emotional disturbances when present are usually the result of seizures in epilepsy and a cause of seizures in migraine. As a result, migraine patients are more elusive than epileptic patients, many victims of headache seeming to cling to their symptoms. Electroencephalographic records are grossly abnormal in epilepsy, and in pain-free periods show doubtful abnormality in migraine. A treatment of dramatic benefit in one of these conditions fails to benefit the other. In epilepsy the essential lesion is a chemical disorder of neurones of the brain leading to a dysrhythmia of their electrical discharge; in migraine the etiology seems to be a dysfunction of the neurovegetative system, leading to abnormal relaxation of cranial arteries and undue stimulation of their sensory nerves. The attacks themselves differ widely in symptomatology — in migraine a gradual onset of hemicranial pain, with gastrointestinal and visual disturbances; in epilepsy a sudden loss of consciousness and involuntary muscular movements.

The principal reason for associating these widely differing phenomena is a generic one: they are inheritance-linked. For many years we at the Neurological Unit have been gathering data from patients with epilepsy and with migraine, and also from samples of the population. I need not wade through a sea of statistics. A few statements will demonstrate the familial coincidence of the two conditions.

Among patients coming for treatment of migraine, the incidence of seizures was twelve times the incidence of seizures in the control group. Among patients coming for treatment of epilepsy the incidence of migraine was nearly twice the incidence of migraine in the control group.

As for the family histories of these patients, among the immediate relatives of migrainous patients epilepsy occurred three and six-tenths times oftener than among the relatives of the control group. Among the immediate relatives of epileptic patients, migraine occurred twice as often as among the relatives of the control group. If the patient had epilepsy, epilepsy was reported in 2.3 per cent of his near relatives. If the patient had migraine, epilepsy was reported in 1.8 per cent of his near relatives. (The incidence of epilepsy in

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the general population is approximately 0.5 per cent.)

One further piece of evidence may be brought forward. If migraine bears a generic relation to epilepsy, the incidence of migraine among the relatives of patients should be greater in the so-called idiopathic epileptic than in the symptomatic epileptic group. To test this point the epileptic patients were divided into two groups, those without and those with evidence of brain injury antedating the onset of seizures. The incidence of migraine in members of the immediate family of the idiopathic group was 3.1 per cent, whereas in the symptomatic group it was only 1.9 per cent. The corresponding incidence of epilepsy among the relatives of the idiopathic group was 2.5 per cent, and of the symptomatic group 1.4 per cent.[1]

This statistical evidence would seem to establish a definite relation between migraine and epilepsy. Obviously the two conditions are not twins, or perhaps even brothers. They are cousins, but not many times removed. Knowledge of one should throw light on the other. Any prohibition against marriage for the purpose of decreasing epilepsy should logically apply to migrainous as well as to epileptic patients.

Treatment Based on Etiology

Discussion of individual treatment cannot be concise and simple, because the causes of epileptic or migrainous seizures are complex and vary in different patients, and in the same patient at different times. I[2, 3] have likened migraine and epilepsy each to a reservoir which periodically fills and overflows its banks, the overflow representing the attack. Each reservoir is fed from underground streams representing both the fundamental and the contributing causes of the attacks.

As has been suggested by the statistics just quoted, the fundamental cause of both epilepsy and migraine is an inherited predisposition to the disorders. The logical prophylactic treatment is eugenic. Effective treatment from this direction has not heretofore been possible, since it is the predisposition and not the disorder itself that is inherited, and since there has been no means of detecting a predisposition to epilepsy or migraine in persons without these symptoms. Recently, however, the Gibbses and I[4] found that 60 per cent of the near relatives of epileptic patients examined presented abnormalities in their cortical electrical records. Relatives with abnormal brain waves outnumbered those with a history of seizures about twenty to one. Therefore, for eugenics to be really effective the twenty persons with cortical dysrhythmia, and not merely the one person with symptoms of epilepsy, should remain single. The same prohibition should apply also to the 10 per cent of the population who are not related to epileptic patients, and who yet have a dysrhythmia presumably indicating a predisposition to epilepsy, or to one of the other clinical disorders characterized by dysrhythmia.

As an offset to this gloomy subject, the important influence of a normal parent should be emphasized. Assuming that 10 per cent of the population have cortical dysrhythmia, by the law of chance only about 1 per cent of married couples would both have dysrhythmia. Yet 35 per cent of the pairs of parents of epileptic patients examined by us exhibited dysrhythmia of both parents. If an epileptic patient will choose a partner whose brain waves are normal, the chance of his having an abnormal descendant is much less than that accompanying the mating of two persons who are without symptoms but have abnormalities of their electroencephalographic records. Thus by use of a laboratory technic the medical profession can answer some of the perplexing questions of heredity. Hope of racial benefit from the application of this new knowledge is limited by the fact that social groups most in need of eugenics do not make use of it.

Even if a predisposition to epilepsy or migraine is present, the syndrome may not appear without the aid of precipitating influences. As has been stated, the character, number and relative importance of these factors vary in different patients. In epileptic patients injury of the brain is most important. Examinations must include procedures designed to disclose lesions of the brain, such as tumors, trauma, meningeal infections and congenital defects. In cases presenting jacksonian seizures (convulsions beginning locally without loss of consciousness), pneumoencephalograms should supplement the routine physical, neurological, spinal-fluid and roentgen-ray skull examinations. When intracranial lesions are demonstrable, the only treatment available is surgical, except that the insufflation of air required in making pneumoencephalograms is sometimes temporarily helpful.

Although the physician's main interest is centered in the brain, he cannot neglect the body, which houses the brain. Improvement in general physique is oftentimes associated with improvement of symptoms. Even less can the social and psychological factors be forgotten. Though the patient may not be rid of his fits, his life may be happy and useful if he is given the opportunity to preserve his self-respect and develop his abilities.

The sufferer from migraine has neither brain

injuries nor social stigmas with which to contend. In the majority of cases the galaxy of symptoms gravitates about the autonomic nervous system and those factors and occasions contributing to "nerve strain." In spite of a heredity that cannot be eradicated, many patients can be rendered symptom-free by removal of worries or fatigue, by lessening emotional stresses or by regulation of habits or improvement of physique. In women, because of the close correlation of headache attacks and menses, the freedom during pregnancy and the permanent relief with menopause, dramatic results might be expected to accrue from administration of hormones or the induction of artificial menopause. The latter expedient usually brings disappointment, but sometimes the administration of large amounts of Theelin seems beneficial.

Treatment by General Measures or Drugs

The items of treatment mentioned are designed to remedy defects in the individual patient uncovered by the thorough study that he or she has supposedly received. Details of treatment for individuals would require more time than I have at my disposal. In addition to the correction of determined defects, there are certain measures that may be tried with all patients.

The study of patients with epilepsy has shown that certain alterations of physicochemical conditions in the body will decrease the liability to seizures. Apparently the changes are not specific, but act by decreasing nervous irritability and thus raising the seizure threshold. These measures are acidosis, dehydration, complete oxygenation and increased concentration of sugar, calcium and carbon dioxide in the blood and brain. Many of these have only laboratory application, but induction of acidosis in children by means of a ketogenic diet is of proved value. Some clinicians have faith also in dehydration, secured by drastic limitation of fluid intake.

Sodium Diphenyl Hydantoinate

Main reliance in the control of seizures has been the use of the sedative drugs, bromides and phenobarbital. Recently, however, Putnam and Merritt[5] have demonstrated the value of sodium diphenyl hydantoinate, a drug which at present answers to the trade name of Dilantin Sodium. This has two points of advantage over bromides or luminal.

First, sodium diphenyl hydantoinate is not a sedative, and therefore its use in maximum doses is not accompanied by the dulling of mental faculties that is often a distressing feature of the drug therapy of epilepsy.

Second, for most patients with epilepsy, and during the two years in which it has been used, this drug has proved more effective than others in the control of seizures. Merritt and Putnam[6] have recorded 227 patients treated for more than two months. Because sodium diphenyl hydantoinate is not equally effective in all types of seizures. they have computed results for the three main types. In patients having psychic, grand-mal and petit-mal seizures the attacks were definitely decreased in 85, 74 and 59 per cent respectively. This improvement was over and above whatever benefit had been obtained by previous treatment — usually with phenobarbital. The favorable results were particularly notable in the case of psychic seizures, which are especially disquieting and may be made worse by heavy phenobarbital medication. On the other hand, relatively few patients with petit mal were benefited, and some were actually made worse.

The administration of sodium diphenyl hydantoinate must be more carefully supervised than that of the sedative drugs. At the beginning one capsule containing 0.1 gm. (1½ gr.) is given three times a day after meals. The amount is slowly increased till the seizures are under control or

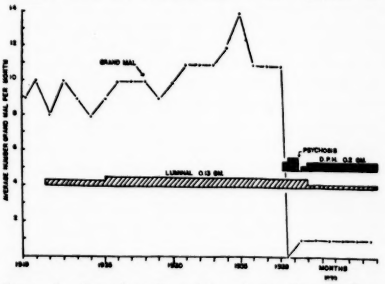

Figure 1. *Record of Convulsions during Twenty Years in Patient C. H.*

The abscissa represents time in years before January, 1939, and in months thereafter. The ordinate represents the average number of grand-mal convulsions per month. Dosage of phenobarbital (luminal) and of sodium diphenyl hydantoinate (Dilantin) is indicated on the chart.

toxic symptoms appear. Six capsules a day seems to be the limit of tolerance. The commonest toxic symptoms are ataxia or tremors, gastric pain or distress, skin rashes, hypertrophy of the gums and psychic upsets. To overcome these untoward symptoms the amount of medicine may need to be temporarily reduced. Persistence will oftentimes carry the patient through temporarily distressing symptoms. Although sodium diphenyl hydantoinate often proves of no benefit, improvement when it does occur may seem miraculous.

A young woman's parents have recorded twenty-two hundred severe convulsions in the course of the last twenty years. As may be seen in the accompanying chart, the number of seizures per year remained remarkably constant and was not influenced by any of the treatments which other physicians and I at various times tried. Phenobarbital was of some benefit and from 1½ to 3 gr. was taken daily throughout the period. In January, 1939, the patient was given 0.3 gm. of sodium diphenyl hydantoinate. Very soon she went into a psychotic state, which persisted for twelve days. Medication was stopped, but was resumed at the rate of 0.2 gm. daily as soon as the psychosis cleared. In the subsequent seven months the patient had only seven convulsions, and her depressed mental state, which I had considered permanent, perceptibly cleared.

Ergotamine Tartrate

In the case of migraine, a drug has in recent years come into use that is equally dramatic in its action.[7, 8] This is ergotamine tartrate, sold under the trade name of Gynergen. In approximately 90 per cent of patients who are having an attack of migraine and who are given a parenteral injection of the drug, the headache and other symptoms disappear as by magic. That the action of the drug is specific, and not merely that of a pain sedative, is proved by the fact that nonmigrainous headaches are not ordinarily benefited by ergotamine.[9] The dose is 0.5 mg., — the contents of an ampule, — injected into a vein, muscle or the subcutaneous tissue at the onset of the symptoms. In 45 per cent of the cases there is associated nausea and vomiting. The occasional patient complains of extreme lassitude or of muscle soreness, or rarely of precordial pain. Ergotamine tartrate comes also in 1-mg. tablets. Five to ten milligrams may be taken in the course of several hours for a headache attack. In addition to the probability of its being vomited, the drug is poorly absorbed from the intestinal tract, and unless the headache is a mild one its termination is not to be expected from oral administration.

During the last three years we have also used a newly isolated alkaloid of ergot called ergonovine. This fraction of ergot is more prompt and potent than ergotamine tartrate in promoting uterine contractions. For migraine, however, the drug is much less dramatic in its therapeutic effect. Of 54 patients given ergonovine by injection, only 39 per cent were completely relieved.[3] However, those patients whose headaches are less stubborn and who have relief from ergonovine prefer it to ergotamine, for the nausea and vomiting are less pronounced. Also, ergonovine is apparently readily absorbed from the gastrointestinal tract, and the minority of patients who are helped by the drug may obtain relief from its oral use. In my series, 21 per cent obtained no relief when ergonovine was injected, and 33 per cent no relief when it was taken by mouth. The proprietary names of ergonovine are various: Ergometrine, Ergobasine Tartrate, Ergotrate, Ergoklonin. Dosages are approximately the same as that for ergotamine tartrate. In the majority of cases, continued use of ergot does not make subsequent headache less severe or less frequent.

Presumably the mechanism of pain production is the same in all patients. The work of Graham and Wolff[10] indicates that relief of migraine headache by ergotamine is attended by coincident decrease in the pulsation of the temporal arteries. Logically help may be expected from surgical interference with the sensory nerve supply to branches of the external carotid artery.

Persistence in Treatment

The physician who undertakes the treatment of either migraine or epilepsy must prepare for a long campaign and must exercise and develop in his patient the gifts of patience, resourcefulness and hope. No matter how happy the patient may be because of the termination of single attacks, the physician has no right to rest on his oars. The eradication of the cause must still be the goal. In the electroencephalogram we have a laboratory measurement of the patient's progress. Probably supervision and treatment should continue so long as brain waves are abnormal. The physician who treats either of these stubborn conditions is justified in offering his patient the consolation of hope. In the last few years, the study of migraine and of epilepsy has brought a better understanding of the mechanisms involved and of new therapeutic agencies. Continued cultivation of this field should yield further fruit.

Summary

The genetic relationship of epilepsy and migraine and certain methods of treatment are discussed, particularly the use of ergotamine tartrate (Gynergen) in migraine and sodium diphenyl hydantoinate (Dilantin Sodium) in epilepsy.

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Discussion

Dr. Carleton R. Metcalf, Concord: Is oxygen of value in migraine?

Dr. Lennox: I think it may be, if given over long periods. You refer, probably, to the report from the Mayo Clinic, where a special type of inhaler has been constructed. In our clinic, Dr. von Storch has secured the apparatus, and finds that certain patients are helped by prolonged inhalation of 100 per cent oxygen. Oxygen causes a constriction of cerebral arterioles, which may explain its beneficial action.

Dr. W. J. P. Dye, Wolfeboro: In the use of ergotamine tartrate, how long does the effect of the drug last and how often does it have to be repeated?

Dr. Lennox: The drug aborts the attack; that is, it stops the pain and other symptoms, and the patient is over that particular attack. It needs to be repeated when the next attack comes along, which may be in a month or may be the next day. When attacks recur several times a week, the doctor is a good deal concerned to know whether repeated doses of ergotamine tartrate might produce arterial spasm and gangrene. We have had no such trouble in our cases, and many of the patients have taken the drug for several years, several times a week and sometimes even daily, without any worse symptoms than some tingling of the fingers. Patients should be observed closely for any effect on blood pressure and on the circulation of the extremities.

A Physician: Does allergy have much effect on migraine, or is its alleged action purely psychological?

Dr. Lennox: Migraine has been defined by some as an allergic condition. We, however, have seen no more allergy in our patients than in the general population, nor have we seen success in treatment along allergic lines. I am not convinced that allergy plays a part either in migraine or in epilepsy.

A Physician: What is the action of Dilantin? Also, can the electroencephalogram of petit mal be differentiated from that of grand mal?

Dr. Lennox: Dilantin does not act as a general sedative; but just how it works is for future research. It has an effect on the electrical waves of the brain, though oftentimes the extent of the improvement of brain waves does not parallel the improvement in symptoms. The electroencephalogram during grand mal is characterized by fast, spiky waves, and during petit mal by alternately fast and slow waves. Behind the different rates of brain waves are differing chemical states of the brain. Patients having only grand mal seem to have a high carbon-dioxide content of arterial blood, and those with only petit mal a low one.

A Physician: Do you think that epileptic patients should be allowed to marry?

Dr. Lennox: The factor of inheritance is probably no greater in epilepsy than it is in diabetes or cancer or perhaps tuberculosis. Epileptic patients should not be singled out. A person with epilepsy may have highly desirable qualities along with it. An epileptic patient has one out of forty near relatives who are epileptic; the non-epileptic patient has one out of two hundred. As I have explained, the normal "carriers" of epilepsy are as important genetically as the epileptic patient. If the latter will choose a mate whose brain waves are normal, the chance of having an epileptic person among his descendants is greatly reduced; this will probably not occur for many generations.

A Physician: Does the water balance have any effect?

Dr. Lennox: Yes. In certain patients, limitation of fluid — the dehydration treatment — seems to be of value.

A Physician: What about the salt-free diet?

Dr. Lennox: That is of value only when giving bromides. With a limited chloride intake, bromides are more readily retained by the body, and therefore not so much bromide needs to be given. A salt-free diet merely reduces the patient's bill at the drugstore.

URINARY INFECTIONS IN INFANTS AND CHILDREN*

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DETROIT

THIS paper proposes to point out some of the important contributions to the knowledge of renal damage resulting from chronic urinary infections, the principal causes of pyuria and urinary infection, the important steps in the diagnostic approach to a patient with pyuria, and an outline of therapy. The recognition of congenital anomalies and infection in the urinary tract has become such a vital part of the diseases of infants and children that it is desirable for us to review certain phases of the problem. The impetus to this situation has developed first and chiefly from the emphasis placed on chronic urinary infections as a cause of renal damage and hypertension in childhood, adolescence or adult life; second, from the development of better methods of diagnostic approach to the genitourinary tract; and third, from the use of the newer therapeutic agents, mandelic acid and sulfanilamide.

Longcope and Winkenwerder[1] were among the first to report hypertension in the uremic stage of cases of chronic pyelonephritis. Butler[2] called attention to the facts that hypertension may be associated with pyelonephritis before there is demonstrable diminution in renal function and that hypertension secondary to unilateral pyelonephritis may disappear after removal of the involved kidney. The problem of hypertension associated with chronic pyelonephritis has been thoroughly studied by Weiss and Parker.[3] These writers emphasized many important facts, such as the following: pyelonephritis is probably responsible for at least 15 or 20 per cent of cases of malignant hypertension; chronic or healed pyelonephritis occurs more frequently than does chronic glomerulonephritis; the hypertension of pyelonephritis can be independent of the activity of the renal infection, and often advances when the disease is in the healed stage; pyelonephritis is one renal disease that lends itself to effective treatment in its incipient stage. The things to remember from these excellent studies are that, first, every patient with an infection in the urinary tract should be subjected to thorough diagnostic study in order to find a possible congenital or acquired cause underlying the infection; second, adequate treatment of the infection and its cause should be instituted; and third, careful follow up of every patient should be maintained, so that a recurrence of the infection may be promptly handled and subsequent renal damage be prevented.

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DIFFERENTIAL DIAGNOSIS OF URINARY INFECTIONS

It is relatively unimportant to elaborate in detail the various clinical conditions that infection in the urinary tract may simulate, as there are many textbooks readily consultable for a complete discussion. The presence of an unexplained fever, abdominal pain, even vomiting or diarrhea, or symptoms referable to the genitourinary tract such as frequency, dribbling, enuresis or painful urination, should lead one to suspect infection in the urinary tract, and to institute proper steps to confirm or rule out such a diagnosis.

URINALYSIS

The finding of leukocytes or bacteria or both in a centrifuged specimen of urine usually suffices to establish the diagnosis of pyuria or infection in the urinary tract. However, this statement must be qualified and analyzed. During the course of many acute infections in locations other than the genitourinary tract, it is not uncommon to find a few leukocytes in the urinary sediment after rapid centrifugation. Certainly such a finding does not signify infection in the urinary tract. The specimen of urine must always be examined immediately after it has been obtained; specimens allowed to stand in open, unsterile containers at room temperature may rapidly develop a heavy growth of contaminating bacteria. Routine urinalysis, performed by a laboratory technician unfamiliar with the patient, may give one a false impression as to the importance of elements in the urine. It is always necessary to examine repeated specimens before establishing the diagnosis of pyuria or infection in the urinary tract, preferably obtained by catheterization in girls and after careful cleansing of the penis in boys. The physician should examine the specimen of urine himself rather than rely on the word of another. It should be remembered that a negative sediment from a single uncentrifuged urine specimen does not exclude the presence of pathologic elements in the urine. In the event that abnormal elements are found in the sediment, anomalies or infection in the vagina or urethra should be excluded before proceeding further with the investigation.

Causes of Pyuria and Urinary Infection

There are many congenital and acquired factors that may be the direct or indirect cause of pyuria and urinary infection. The most important of them are as follows:

Pyelonephritis
Hydronephrosis
Calculi in the kidney, ureter, bladder or urethra
Renal tuberculosis
Renal tumor
Perirenal infection, such as tuberculosis of the spine
Aberrant vessel obstructing the ureter or some other portion of the urinary tract
Ureteral kink
Periurethral infection
Hydroureter
Ureteral stricture
Diverticulum of bladder or urethra
Neuromuscular disease of bladder
Congenital valves at the ureteral orifices
Ureteral meatus stricture
Bladder tumor
Cystitis
Obstruction of the neck of the bladder
Prostatitis
Hypertrophy of the verumontanum
Congenital valves in the posterior urethra
Periurethral infection
Urethritis and stricture
Stenosis of the prepuce or urethra
Cervicitis
Foreign body in the vagina
Vaginitis

Diagnosis of Pyuria and Urinary Infection

The first step in securing information as to the presence of a urinary infection, after excluding anomalies or infection of or about the external genitalia, is to obtain a catheterized specimen of urine for microscopic examination and culture in order to determine the causative organism. Catheterization will furnish information as to the volume of residual urine, and may help to exclude the presence of a posterior urethral anomaly.

The next step is to secure a flat roentgenogram of the abdomen, including the bladder. This procedure may give information as to the size of the kidneys, and the presence of large intra-abdominal masses or calculi in the urinary tract. As a measure of kidney function, valuable information may be secured by determining the blood pressure and the nonprotein nitrogen in the blood.

These procedures may be quite adequate if the infection is the initial attack or is secondary to some other infection such as pneumonia; but in the event of recurrent attacks of infection, or an infection of long duration, further studies of the urinary tract and function of the kidneys are desirable. These should include a test for the concentrating power of the kidneys and an intravenous pyelogram; if evidence is at hand of diminished kidney function or anomalies in the urinary tract, it may be necessary to obtain a urea clearance test, and to perform a cystoscopy and obtain retrograde pyelograms. If the infection is the patient's first attack, and it has been demonstrated that the kidneys have normal concentrating ability and that the blood nonprotein nitrogen, blood pressure and intravenous pyelograms are normal, medical treatment may be instituted without performing cystoscopy and retrograde pyelography.

If unsatisfactory evidence has been obtained from intravenous pyelography, a cystogram may be done prior to retrograde pyelography. Information may be secured from this procedure as to the presence of a diverticulum of the bladder, tumor of the bladder or posturethral obstruction.

Indications for cystoscopy may include evidence from intravenous pyelography of impaired function of one kidney or a portion of a kidney, absence of a part of the urinary tract, evidence of an anomaly of the bladder or urethra, and the necessity of examining and culturing the urine and determining the function of each kidney separately. However, if inoperable bilateral anomalies or abnormalities are observed in the intravenous pyelograms, or if the kidney function is markedly diminished, cystoscopy may be contraindicated.

In order to obtain successful intravenous pyelograms in children, certain general principles must be followed. It is necessary to restrict the fluid intake for some hours preceding injection of the dye so as to obtain a specific gravity of at least 1.020 in the urine, in order that the dye may be sufficiently concentrated to give proper visualization of the urinary tract. The presence of an excess amount of gas in the small intestine will obscure the dye in the urinary tract, and measures must be taken, such as mild laxatives, cleansing enemas or even drugs, to increase intestinal peristalsis and control excessive amounts of gas. A roentgenogram of the abdomen should be taken prior to injection of the dye, and if excessive amounts of gas are seen the procedure should be postponed until the gas can be eliminated. The dose of the intravenous dye should be adequate, and it should be remembered that the dose for infants is larger than that for older children.

The following list presents in summarized form the essential diagnostic procedures in the study of a patient with pyuria or urinary infection:

1. Examination of the external genitalia for the presence of congenital anomalies, inflammation, purulent discharge or foreign body.
2. Urinalysis (voided specimen, unless the patient is a girl with a vaginal discharge).
3. Catheterization (urethral anomalies, residual urine, urinalysis and culture of urine).

4. Kidney function tests.
   a. Blood pressure.
   b. Concentration test (the specific gravity of the urine should be at least 1.020).
   c. Nonprotein nitrogen of the blood.
   d. Urea clearance test if *a*, *b* or *c* are abnormal.
5. Roentgenogram of the abdomen.
6. Intravenous pyelogram.
7. Cystogram (especially if bladder abnormalities are suspected).
8. Cystoscopy.
   a. Appearance of the urethra and bladder.
   b. Ureteral catheterization, to determine the function of each kidney separately; culture and examination of urine from each kidney separately.
   c. Instillation of dye for roentgenograms.

The importance of the early recognition and treatment of congenital anomalies producing obstruction in the urinary tract and subsequent renal damage should be emphasized. The following case demonstrates how rapidly renal damage may occur following an obstructing congenital anomaly.

W. B., a male infant, 3 months of age, was admitted to the hospital on June 20, 1939, with the chief complaints of difficulty in feeding and increasing pallor of the skin since birth. The birth was normal, and the birth weight was 8 pounds. The patient was given an evaporated milk formula but frequently refused it. Vomiting occasionally occurred after the feeding. Several changes were made in the formula, but the refusal and vomiting continued. The mother noted that the infant's skin had become increasingly pale since birth and that he seemed "feverish" frequently during the month preceding admission. Two weeks prior to entry a severe cough developed, which was spasmodic in character and was occasionally followed by vomiting. The infant seemed to be dyspneic for about 2 weeks prior to entry.

Physical examination revealed a fairly well-nourished infant with marked pallor of the skin who appeared acutely ill. The weight was 11½ pounds. The respiratory rate was increased, and the rectal temperature 101°F. The remainder of the physical examination was essentially negative except the abdomen. In the latter there was moderate distention, and a large, smooth, hard mass, which did not move with respiration, was palpable in the right flank. The tip of the spleen was palpated at the left costal margin.

Urinalysis (voided specimen) showed a clear, yellow urine without the presence of albumin, sugar or acetone, and no leukocytes, erythrocytes or casts in the sediment.

Examination of the blood revealed the presence of a severe secondary anemia. Other laboratory procedures were negative.

A roentgenogram of the chest showed considerable pneumonic infiltration in the central lung fields, with extension into both upper lobes. A film of the abdomen was unsatisfactory owing to obscuration by distended loops of intestine.

The patient received a blood transfusion the day following admission, and treatment of the pneumonia with sulfapyridine was instituted. However, his condition became steadily worse. The signs of pneumonia progressed. The rectal temperature varied between 99 and 105°F. It was suspected that the mass palpated in the right flank was an enlarged kidney, but because of the gravity of the condition, further diagnostic procedures, such as kidney visualization and renal function tests, were not attempted. Death occurred on the 5th day.

An autopsy revealed the presence of enlarged kidneys, the right being larger than the left, and on section extensive hydronephrosis and pyonephrosis were seen, with almost complete destruction of the substance of the kidney. Both ureters were markedly dilated and the bladder wall was hypertrophied. On section of the posterior urethra the verumontanum was found to be hypertrophied and practically filled the lumen of the urethra. The lungs showed extensive bilateral pneumonic infiltration and patches of consolidation.

Although the immediate cause of death in this patient was the pneumonia, undoubtedly the obstruction in the urethra was the primary factor in the chain of events leading to the chronic urinary obstruction and infection, the renal destruction, the secondary anemia and, finally, the pulmonary infection and death. An interesting and important point for emphasis was the normal urinalysis on the day of admission. This confusing finding may occasionally occur, and demonstrates the necessity of repeated examinations of the urine before excluding the diagnosis of pyuria.

Treatment of Urinary Infections

Many drugs have been used in the treatment of infections in the urinary tract. With the advent of mandelic acid and sulfanilamide these drugs have almost entirely replaced the older urinary antiseptics, and most of the latter are now only of historical interest. Both sulfanilamide and mandelic acid are necessary in therapy, as each drug possesses peculiar advantages.

In considering the use of mandelic acid it is necessary to remember that prolonged urinary infection or the presence of congenital abnormalities in the urinary tract may result in marked renal damage; this in turn will not allow sufficient concentration of the urine, and the proper degree of urine acidity will not be attained. The drug is administered in the form of a 10 per cent elixir of ammonium mandelate. The total daily dose is estimated so that a 1 per cent concentration of mandelic acid in the urine may be constantly maintained. It is necessary to restrict the fluid intake of the patient in order to maintain this concentration. Table 1 shows the fluid restriction and daily dose of mandelic acid for various age groups.

Table 1. *Dosage of Mandelic Acid and Fluid Restriction According to Age.*

Age	Total Fluid Each 24 Hours	Mandelic Acid (Daily Dose)
yr.	*cc.*	*gm.*
Under 1	450	3
1–2	500	4
3–6	500	5
6–9	600	6
9–12	800	8

The acidity of the urine should be checked daily in order to make sure that the pH is at the necessary level of 5.5 or below, using chlorphenol red as the indicator. Occasionally it may be necessary to supplement the mandelic acid with a daily dose of an acid salt, such as ammonium chloride, in order to obtain a urine that is sufficiently acid. The sediment of a centrifuged specimen should be examined daily to detect the appearance of erythrocytes or casts. If these elements appear, having been previously absent, an irritant effect of the mandelic acid on the kidney may be occurring and the dose of the drug must be reduced or discontinued promptly. The mandelic acid should be continued for at least a week after the urine culture has become sterile. A limit of three weeks is placed on the continuation of therapy, because if sterilization of the urine has not occurred within this time it is not likely to occur by prolongation of therapy. Mandelic acid is effective against infections caused by organisms of the colon bacillus group and by *Streptococcus faecalis*. The drug is not effective against infection due to *Bacillus proteus*, because this organism is always accompanied by an alkaline urine, and it is impossible to attain the proper acidity of the urine necessary for bactericidal action by the mandelic acid.

Sulfanilamide should be administered orally, accompanied by equal or larger doses of sodium bicarbonate. The dosage of sulfanilamide is usually 1 gr. per pound of body weight every twenty-four hours. It is desirable to attain a concentration of free sulfanilamide in the urine of 100 to 300 mg. per 100 cc., and to maintain the alkalinity of the urine at pH 7.4 or above. The pH can be easily checked by testing a specimen of urine with phenol red as the indicator. As it is difficult to obtain complete twenty-four-hour collections of urine from infants and small children for sulfanilamide determination, it is simpler to maintain the blood concentration of free sulfanilamide at a level of 10 to 12 mg. per 100 cc. A slight restriction of the fluid intake is desirable in order to maintain the correct urine concentration of sulfanilamide. In infants the daily fluids should be limited to 400 or 500 cc., and in older children to 1000 or 1200 cc. A culture of the urine should be obtained about three days after the sulfanilamide has been started, and at intervals of two or three days until the culture remains sterile. The full dosage should be maintained for at least two days after the culture becomes sterile, then decreased to about half the original amount, and continued for two or three days in order to prevent recurrence of the infection. The patient should be observed daily for evidence of toxic reactions to the sulfanilamide, such as fever, a skin rash, hemolytic anemia, leukopenia, headache and mental confusion, nausea and vomiting and abdominal pain. If any of these reactions occur, it is desirable either to reduce the dose of the sulfanilamide or to discontinue it. Sulfanilamide is effective against infections caused by organisms of the colon bacillus group, staphylococci, beta hemolytic streptococci, *B. proteus* and a few strains of *Streptococcus faecalis*. Sulfanilamide has one distinct advantage over mandelic acid in that it may be administered during the acute febrile stage of the urinary infection.

A brief summary of the dosage and plan of administration of sulfanilamide is as follows:

Dose of sulfanilamide: 1 gr. per pound of body weight every 24 hours.

Dose of sodium bicarbonate: 1 gr. or more per pound of body weight every 24 hours.

Total fluid intake every 24 hours:
Infants, not over 400 to 500 cc.
Children, not over 1000 to 1200 cc.

Urine pH: 7.4 or higher.

Sulfanilamide concentrations:
Urine, 100 to 300 mg. per 100 cc.
Blood, 10 to 12 mg. per 100 cc.

Summary

Neglected cases of pyuria and urinary infection may result in severe renal damage and malignant hypertension.

The diagnosis of pyuria or infection in the urinary tract must be made with proper clinical and laboratory procedures.

Completeness of examination of the genitourinary tract must be emphasized.

Adequate therapy of the urinary infection with mandelic acid or sulfanilamide or both, following proper bacteriological study of the organism responsible for the infection, must be instituted, and maintained until repeated cultures of the urine prove that the infection is cured.

Thorough follow-up of patients examined and treated for urinary infections must be maintained. Recurrences of the infection may occur even after apparent successful treatment, and it is important to relieve the kidneys of further assaults as promptly as possible.

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INGUINAL HERNIORRHAPHY IN THE AGED*

An Analysis of One Hundred Consecutive Cases In Patients Over Sixty-Five Years of Age

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IN A previous communication,[1] attention was called to the rapid increase in the proportion of aged persons in the population and to the fact that, in the near future, an increasing number of aged individuals can be expected to present themselves with conditions requiring surgical treatment.

Inguinal hernia, since not only its frequency but its danger increases considerably with each decade (Figs. 1, 2 and 3), becomes a surgical condition of particular interest in the aged. Also, the analysis of a series of cases is facilitated by the standardization of the operative procedures employed in its repair.

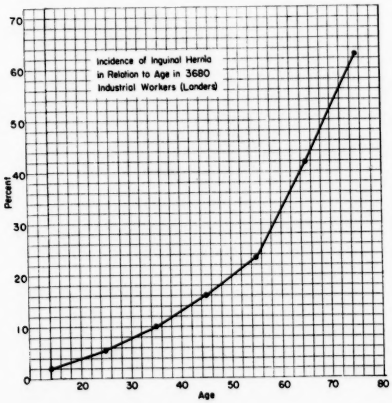

FIGURE 1.

Curve constructed from figures given by Landers (Age incidence of hernia. Indust. Med. *7:671, 1938).*

One hundred consecutive cases in patients over the age of sixty-five were studied from the records of the Peter Bent Brigham Hospital. The average age was 69.8 years. The series included 96 men and 4 women. One hundred and thirty-four hernias were repaired in one hundred and ten operations through one hundred and thirty incisions. There were almost exactly the same number of right and left hernias. The proportion of indirect to direct was approximately two to one. Eight were recurrences after previous operations. In 30 cases there were bilateral hernias. Four sliding hernias occurred in the series — three left and one right. One operative death occurred, due to pulmonary embolism. The patient, a seventy-five-year-old man, succumbed on the twenty-third day after the second of two elective operations carried out under local anesthesia for bilateral hernias. There had been symptoms of pulmonary infarction on the tenth and eighteenth days. The diagnosis was confirmed by necropsy.

In 10 cases operation was imperative, for incarceration in 7 and for strangulation in 3. All the patients recovered; only 3 developed complications: one developed a severe cough, in another case the wound became tender and indurated, and the third patient was disoriented for twenty-four hours after operation.

With regard to the remaining 90 patients, for whom operation was an elective procedure, the reasons for seeking surgical aid are of interest. Twenty of these were undoubtedly influenced by one or more episodes of incarceration, but for the great majority the hernia appears to have become simply an intolerable chronic inconvenience. Of 67 patients who had worn a succession of trusses for an average of 9.4 years, only 12 were satisfied with their appliances at the time of admission to the hospital. In one case the truss had produced a considerable degree of ulceration of the skin. Although operation was delayed until this had healed, the patient developed the only gross wound infection in the series.

In many cases the annoyance of the hernia, from the patient's point of view, outweighed the manifestations of much more serious disease. This is well illustrated by the following case:

J. Y., a 73-year-old laborer, was referred to the Medical Service for the treatment of decompensated heart disease. On admission there was found to be marked enlargement of the heart, auricular fibrillation, pulmonary congestion and peripheral edema. The blood pressure was 200/110. There was also a football-sized, right, direct hernia, which was difficult to reduce. Two weeks after admission, improved by rest and digitalization, the patient requested that the hernia be repaired, since it had always been an encumbrance and no truss had ever kept it reduced. After some deliberation operation was carried out under local anesthesia. At the time of operation, fibrillation, pulmo-

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nary congestion and peripheral edema were still present. The procedure required more than 2 hours. Fine silk sutures were used throughout. The postoperative course was entirely uneventful, save for mild disorientation for about 24 hours. The patient was discharged, improved, 20 days after operation. Death due to cardiac failure occurred suddenly 6 months later. There was no recurrence of the hernia.

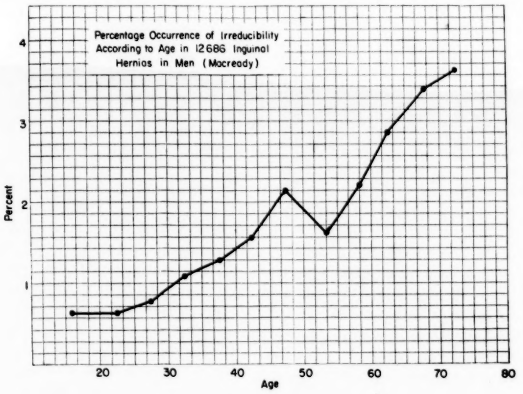

FIGURE 2.

Chart constructed from figures given by Macready (A Treatise on Ruptures. *442 pp. Philadelphia: Blakiston, Son & Co., 1893).*

Any consideration of surgery in the aged must involve a careful evaluation of chronic or degenerative disease other than that for which operation is performed. Only 15 of the 100 patients studied were found to be entirely free from other disease. One hundred and twenty-five chronic or degenerative illnesses were distributed among the remaining 85 patients. These are listed in Table 1, together with the postoperative complications that could reasonably be attributed to them. The great majority could be classified among benign prostatic hypertrophy (or a history of previous prostatectomy), cardiovascular degeneration and chronic pulmonary disease, all with relatively few referable postoperative complications. Included in the 36 cases of miscellaneous disease are sixteen diseases ranging from diabetes mellitus to hemachromatosis. Nine, or 25 per cent, of these patients developed referable postoperative complications.

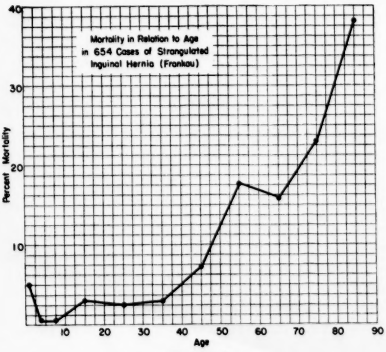

FIGURE 3.

Chart constructed from figures given by Frankau (Strangulated hernia: a review of fourteen hundred and eighty-seven cases. Brit. J. Surg. *19:176–191, 1931).*

TABLE 1. *Relation of Concomitant Disease to Postoperative Complications.*

CONCOMITANT DISEASE	NO. OF CASES	REFERABLE POSTOPERATIVE COMPLICATIONS	
		NO. OF CASES	PERCENTAGE
Benign prostatic hypertrophy (or previous prostatectomy)	40	3	8
Cardiovascular degeneration	26	3	12
Chronic pulmonary disease	23	2	9
Miscellaneous	36	9	25

Local novocain was the most frequently employed anesthetic in the series, and had the lowest incidence of postoperative complications. Nitrous oxide and oxygen, ether and spinal novocain followed in order of usage (Table 2). There was no correlation between the use of novocain and wound infections, possibly because nerve blocking, after the method of Cushing,[2] was almost invaria-

bly practiced, rather than infiltration of the tissues at the operative site. Ether was used for both the patients in the series who developed septic wounds.

The appendix was removed three times without complications. Orchidectomy was carried out five times; one patient developed a small scrotal hematoma. Autogenous fascia was used eight times in the repair of a hernia. One of these patients developed a thrombophlebitis.

In 2 cases, herniorrhaphy was carried out at the same time as perineal prostatectomy. One of these patients developed ecchymosis of the scrotum, and the other was irrational for the first twenty-four hours after operation. In 2 other cases herniorrhaphy was carried out during convalescence from prostatectomy, and 1 patient's hernia was repaired while he was being prepared for prostatectomy. None of these patients developed complications. Hemorrhoidectomy was performed immediately after herniorrhaphy in 1 case without event. It would seem unwise to combine herniorrhaphy with other major surgery, but at the same time there does not appear to be any advantage in operating on multiple hernias in stages. In fact, the dangers of prolonged recumbency, notably bronchopneumonia and thromboembolic disease, may outweigh the possible advantages of avoiding a prolonged operation. Nine of the 30 patients who had bilateral hernias, or combinations of hernias requiring operation on both groins, were operated on in two stages. Five, or 55 per cent, developed complications, 1 terminating fatally. Exactly the same percentage of complications developed in the remaining 21 patients whose hernias were repaired at a single operation.

Table 2. *Anesthesia in Relation to Postoperative Complications.*

Anesthetic	No. of Operations	Total Postoperative Complications		Postoperative Complications Referable to Anesthetic	
		No.	Per-centage	No.	Per-centage
Local novocain	58	19	33	3	5
Ether	21	13	62	3	14
Nitrous oxide and oxygen	15	6	40	1	7
Spinal novocain	14	7	50	2	14

Excision of a hydrocele was combined with herniorrhaphy in 10 cases. Five of these patients developed wound complications — 2 suppurative and 3 nonsuppurative. In both the former and 2 of the latter, catgut sutures were used throughout. In no operation in which fine silk was used was there a suppurative complication. In fact, of all the factors associated with the operation which might contribute to postoperative wound complications, the suture material was found to be the most important. There were nearly three times as many non-septic and septic wound complications when catgut was used as when fine silk was employed (Table 3).

Table 4. *Complications.*

Complication	No. of Cases	Complication	No. of Cases
Gross infection	1	Thrombophlebitis	2
Superficial infection	1	Lymphangitis of lower leg	1
Induration of wound	5	Angina pectoris	1
Hematoma of wound	3	Auricular fibrillation	1
Hematocele	3	Cerebral hemorrhage	1
Edema of testis or cord	2	Cholangitis	1
Massive pulmonary collapse	1	Insulin reaction	1
Pulmonary embolism (fatal)	1	Peptic ulcer pain	1
Pulmonary infarction	1	Urinary retention (requiring catheterization)	7
Severe cough	1	Psychosis or disorientation	7
Severe hiccough	1		
Abdominal distention	3	Total	46

Forty-six postoperative complications occurred in 41 patients, as shown in Table 4. While many of these complications may seem trivial and unrelated to the operation, it seemed wisest to include everything that disturbed the postoperative course in the slightest as being at least potentially dangerous in this age group. No correlation could be discovered between complications and operating time, the type of operation or the experience of the surgeon. The low incidence of pulmonary complications is probably fortuitous, since the average time spent in bed after operation was fourteen days. However, activity in bed was encouraged and breathing exercises were frequently employed.

The frequency of postoperative disorientation

Table 3. *Suture Material in Relation to Complications and Recurrence.*

Suture Material	No. of Cases	No. of Hernias	No. of Incisions	No. of Hernias Examined after 1 Year	Recurrences		Cases Developing Complications of Any Type		Wound Complications			
					No.	Percentage	No.	Percentage	Septic	Non-septic	Total	Percentage
Silk	58*	76	73	45	3	7	23	41	0	5	5	7
Catgut	39*	53	52	29	5	17	16	43	2	7	9	17
Mixed	5	5	5	2	0	0	2	40	0	1	1	20
Totals	100	134	130	76	8		41		2	13	15	
Averages						11		41				11

*Two patients had silk sutures on one side and catgut on the other.

appears to be related to preoperative medication. Of the 7 patients exhibiting this complication, 5 were operated on under local or spinal novocain, reinforced with relatively large doses of morphine, scopolamine or barbiturates.

Contact was made with 79 patients one year or more after operation. Twenty-four of these replied by mail that they had been benefited by operation and had no evidence of recurrence. This was regarded as highly unlikely, if not impossible, and therefore only the remaining 55 patients who were examined one year or more after operation by a member of the staff of the hospital were considered. There were eight recurrences (11 per cent) among the 76 hernias repaired in these patients, four direct and four indirect.

No correlation could be found between the incidence of recurrence and concomitant disease, the experience of the surgeon, the anesthetic or the age, weight or blood pressure of the patient. No recurrences developed among the patients who were operated on for incarceration or strangulation. More than twice as many recurrences occurred among the patients who developed postoperative complications (17 per cent) as among those whose convalescence was uneventful (7 per cent). Neither of the patients whose wounds became septic suffered a recurrence. The type of operation was apparently a factor in recurrence (Table 5). However, the radical Halsted procedure with subcutaneous transplantation of the cord was employed most frequently in patients with poor musculature and fascia, and therefore with a greater possibility of recurrence.

TABLE 5. *Type of Operation in Relation to Recurrence.*

Operation	No. of Hernias	No. Examined after 1 Year	Recurrences	
			No.	Percentage
Ferguson	39	24	3	13
Bassini	44	26	1	4
Halsted	47	26	4	15
Totals	130	76	8	
Average				11

The most important single factor in recurrence appeared to be the suture material. The percentage of recurrence was nearly three times as great when catgut was used as when fine silk was employed (Table 3).

Comment

Grace and Johnson[3] have pointed out that there is very little accurate information available concerning the results of herniorrhaphy in patients over fifty. They report 1032 patients with an incidence of infection of 4.95 per cent and a recurrence rate of 26.6 per cent. Brooks[4] has reported 20 patients of seventy or older with 1 death. Dulin[5] concludes that the repair of inguinal hernia in the aged is not only relatively dangerous but unsatisfactory. He reports 301 patients sixty or older with a recurrence rate of 20.5 per cent and a mortality rate of 3.8 per cent. He found that 8.0 per cent of wounds became infected when local anesthesia was used, and 2.3 per cent when spinal anesthesia or nitrous oxide and oxygen was used. Sutures of No. 3 and No. 2 chromic catgut were used exclusively in this series.

The great importance of the suture material in relation to complications and recurrence after herniorrhaphy is now generally recognized. The recent experimental work of Meleney,[6] Shambaugh and Dunphy,[7] and others has been amply confirmed by such clinical studies as those of Parsons,[8] Beekman and Sullivan,[9] Burdick, Gillespie and Higinbotham[10] and Shambaugh.[11] In every case the teachings of Halsted[12] have been vindicated, and fine silk has been found to be from every point of view the best suture material. The present study, although based on a relatively small number of cases, provides further evidence in support of this teaching, and demonstrates that inguinal herniorrhaphy, whether elective or imperative, is a reasonably safe and satisfactory procedure for the aged patient.

Summary

One hundred consecutive cases were studied in which operation for inguinal hernia was carried out at the age of sixty-five or older. In 10 cases the operation was an imperative or emergency procedure; in the remaining 90 it was elective.

The operative mortality of the series was 1 per cent. One and seven-tenths per cent of the one hundred and thirty incisions became infected. Ten and eight-tenths per cent of seventy-six hernias examined one year or more after operation recurred.

Nearly three times as many wound complications and recurrences occurred when catgut was used as when fine silk was employed.

The same incidence of complications followed the repair of multiple hernias in stages as in a single operation.

Novocain nerve-block anesthesia was followed by the lowest incidence of postoperative complications. The Bassini type of operation was the most satisfactory from the point of view of recurrence. There was no correlation between the incidence of complications or recurrence and operating time, the experience of the surgeon, concomitant disease and the age, weight or blood pressure of the patient.

Inguinal herniorrhaphy, whether elective or imperative, is a safe and satisfactory procedure for the

aged patient when carried out under novocain nerve-block anesthesia, with the minimum of preoperative medication and with fine silk as the suture material.

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CHRONIC BRUCELLOSIS*

1. The Incidence of Chronic Undulant Fever in Rhode Island

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A STUDY of over 4000 individuals in Rhode Island during the past four and a half years has revealed in 441, or about 10 per cent, clinical and laboratory evidence supporting a diagnosis of chronic brucellosis.§ Seven hundred and ninety-nine (18 per cent) had positive reactions to one of the following three tests: intradermal, intramuscular, agglutination. The 441 who had clinical evidence of chronic brucellosis showed positive reactions to at least two of these tests.

A positive reaction to any of the tests used in making a diagnosis of undulant fever should make one suspicious of its presence. According to Evans, Robinson and Baumgartner,[1] a positive agglutination test is more reliable than a positive skin reaction. They found the opsonocytophagic reaction to be the least reliable of the specific tests, of which the intracutaneous test is probably the least standardized. Various antigens have been used, such as heat-killed bacteria, a filtrate of an extract of the ground bacterial cells, a filtrate of old cultures and a lipoid-free antigen. Moreover, the amount and dilutions used for testing have not been uniform. In spite of these differences, the percentage of positive reactions has been high in the skin tests, as well as in the other tests used in various sections of this country. It is generally recognized that the greater and more frequent the contact which man has with infected animals, the greater the percentage of positive reactions, no matter which of the tests is used.

Goldstein, Fox and Carpenter[2] found that 10.1 per cent of 332 unselected hospital patients gave positive intradermal reactions. They used a clear culture filtrate containing 13.3 mg. of nitrogen per 100 cc., injecting 0.1 cc. of a 1:100 dilution. Angle, Algie, Baumgartner and Lunsford[3] obtained positive reactions in 9 per cent of 7122 school children. They used Huddleson's "brucellergin" for the intradermal tests.[3, 4] They found, moreover, an increasing percentage of positive cutaneous reactors in successive age groups up to early adulthood. The lowest percentage of positive reactions was found in negro children. Levin[5] tested 365 individuals, and found that of the 27 (7 per cent) having positive skin reactions, 15 showed clinical evidence of chronic brucellosis. He used a fat-free ground bacterial suspension containing 0.004 mg. dry bacterial protein per 0.2 cc. Meyer and Geiger[6] found cutaneous reactions in 10 per cent of a group of medical students and in 60 per cent of a group of veterinarians. Gersh and Mugrage[7] submitted 491 hospital patients to the skin test and obtained positive reactions in 12 per cent. This was a much higher percentage than he found in the agglutination test, which was positive in only 1.2 per cent of 5000 cases.

There have been a number of reports on agglutination tests for the presence of brucella antibodies. A few of these are given to indicate the wide variation. Hunt and Noll[8] found that 8.9 per cent were positive in 1000 samples of blood serum tested. They considered reactions below a 1:80 dilution without significance. Giordano and Ableson[9] carried out agglutination tests on 1100 human serums which had been submitted for Widal or Wassermann tests or for chemical analysis, and found that 5.7 per cent had positive tests. Dolman and Hudson[10] tested 5068 specimens of

*This is the first of a series of articles on chronic brucellosis.

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§The clinical findings in these cases will be discussed in a later paper.

blood and obtained 4.5 per cent positive agglutinations.

At the Rhode Island Hospital during 1937 and 1938, 372 serums sent to the laboratory for a Widal test were also tested for brucella agglutination, using a commercial antigen. Of this group, 12 per cent had positive reactions in dilutions of 1:40 or higher, and 9 per cent in dilutions of 1:80 or higher. However, only 78 cases of acute undulant fever have been reported in Rhode Island for the decade ending January, 1939.

Rhode Island is primarily an industrial state, only 1.3 per cent of its population being engaged in agriculture, as compared with 10.6 per cent in Vermont.[11, 12] During the latter part of 1937, 62 per cent of the Rhode Island milk supply was produced at home, 20 per cent came from Connecticut, 16 per cent from Massachusetts and 2 per cent from Vermont.[13] Of the total milk supply available for sale in Rhode Island 76 per cent is produced for pasteurization and 24 per cent for sale as raw milk.[13] In Providence in 1937, 92 per cent of the total milk sold was pasteurized and 8 per cent was raw. In Newport the percentage of pasteurized milk is even higher.[14] All the milk imported from Vermont is pasteurized either at the source or within Rhode Island.

From May, 1936, to May, 1937, approximately 10 per cent of the cattle in Rhode Island were tested for Bang's disease. Approximately 10 per cent of those tested proved to be positive; an additional 10 per cent were suspicious.[13] Because of the unusual characteristics of the brucella organisms and the ease with which all food produce, including meats, eggs, butter, ice-cream, cheese, milk, fruits and vegetables may become contaminated, it is evident that milk should not be regarded as the commonest source of infection.[15, 16] Except in rare cases where mastitis is present, the organisms are not found in the milk even when the cows are known to be infected. The milk may, of course, be contaminated by careless handling. Brucella organisms have been isolated from hens, and all domestic animals have been shown to be carriers of this disease.[15–17] It has also been found that the organisms may survive for a year or more in manure stored under ordinary New England farm conditions. There is no evidence, however, that they multiply except in infected animals. The prevalence of the brucella organism suggests that the infection may be almost universal in a given community and that only certain individuals become chronically ill.

Within the last two years the literature has been rich in articles dealing with the incidence, diagnostic procedures and treatment of various forms of infection with the brucella organism in man. At the present time the nomenclature is rather confusing because the term "undulant fever" represents only those infections showing the characteristic temperature changes. In this country the typical undulating type of temperature in the acute infection is rarely seen. So far as our own experience is concerned, only 1 case showing the typical undulating fever has been encountered.

The clinical picture and course of the usual acute form of this infection is familiar to all and has been adequately described. There is, however, a mass of evidence supporting the contention that there is a definite chronic form of this infection in human beings, to which the term "brucellosis" may well be applied.

Nearly all the recent studies dealing with the diagnosis and incidence of chronic brucella infections have been carried on in groups of university students or school children, or the inhabitants of various institutions that include the chronically ill in the later decades of life. In general, the incidence of this disease, in all groups studied, is in the neighborhood of 10 per cent. This figure is about that found in our group of private patients. It also holds true in our studies made of groups from outpatient departments, the medical wards, almshouse inmates and patients in a hospital for chronic mental diseases, where the same technic was used.

The present study of private cases deals with the people encountered in a practice limited to internal medicine, and obviously with a group of patients who voluntarily seek medical aid. The general relation between chronic brucellosis and personal allergy is significant. Of the private cases studied, 92 per cent had a history of allergy and all had a history of allergy in their immediate families. Those people showing active symptoms of the chronic infection are probably suffering from a hypersensitivity to *Brucella abortus*. The clinical behavior of these cases, when under treatment, indicates an allergic state rather than a lowered resistance. The reactions to varying concentrations of antigen solutions used in the intradermal test are consistent with a hypersensitive state. Individuals highly sensitive may react negatively to a strong antigen solution, but show a strongly positive intradermal reaction if very dilute solutions are used. This fact has also been observed by us in the intradermal reactions to solutions of various drugs, chemicals, alkaloids and bacterial proteins. Possibly this explains a part, at least, of the often reported discrepancies between intradermal and serum agglutination tests. The patients' chief complaints, many times, have no apparent relation to this infection, but it must be remembered that as a group they are not well people. It is quite to be expected

that figures derived from such a group would not agree entirely with those obtained from groups of students or from studies made on blood sent to the laboratory for the Wassermann or Widal test.

In this study, besides the clinical evidence, three distinct tests were used in establishing the diagnosis: the intradermal test, the serum agglutination test and the intramuscular test.

The serum agglutination test, carried out on all cases regardless of history or clinical findings, was essentially that described by Carpenter, Boak and Chapman,[16] with the following alterations: depression slides with sealed cover glasses were used instead of tubes. We found the wire loop for preparing the various dilutions, if handled with reasonable care, more rapid than and practically as satisfactory as the capillary pipettes or the rheometer. Sterile saline solution (0.85 per cent) was used for diluting fluid. All the glassware was chemically clean and sterile. The preparations were sealed with heavy oil, care being taken to prevent any contamination of the preparation. The work was carried out as rapidly as possible without interfering with accuracy, in order to prevent evaporation of the solutions. We found this necessary, for in tests carried out in overheated rooms or with opened windows and strong drafts, or with slow technic, evaporation sometimes altered the results in the more dilute preparations by over 25 per cent by the time the readings were made. Because of this no reliance was placed on any open-slide method.

With a little experience the depression slide technic proved to be a timesaver. A larger number of tests can be incubated in a much smaller space than is necessary for the tube technic. Instead of a series of dilutions from 1:15 to 1:405, the dilutions were carried on to about 1:10,000. Also, a series of slides was prepared in a similar manner but with the antigen diluted in one series to 1:10 and in another to 1:100, the serum dilutions being as in the first series. Also, a series was prepared using similar dilutions of serum and antigen. Thus all combinations of various dilutions of both antigen and serum are represented. Occasionally agglutination occurs only in higher dilutions of both antigen and serum. The result of a test varies depending on the time in the cycle of antibody production at which the sample is taken. We found many individuals showing a rather cyclic rise and fall in the serum titer. There may be in the host a variation in the degree of absorption of antigenic substances, or the response of the individual may be the variable factor. When this fact was established, a system of taking repeated specimens at two-week intervals was adopted, and if three negatives were obtained, two more specimens were taken at three-week intervals. In some cases, positive tests were obtained only in this manner. Dilutions of 1:40 or higher were considered positive if one of the other tests was also positive.

The solution used for the intradermal test was a very dilute, fat-free aqueous solution derived from ground, heat-killed *Brucella abortus* (bovine, caprine and suis in equal proportions). The three dilutions used represented a protein solution equivalent to suspensions of 250,000, 25,000, and 2500 bacteria per cubic centimeter. Only 0.02 cc. of each dilution was injected intradermally; thus the doses used represented, in protein, the equivalent of 5000, 500 and 50 bacteria respectively. In a few of the obviously severe cases, even more dilute solutions were used. The amount used was minute, but in very sensitive cases small areas of superficial slough occurred even with the smallest doses. Often pigmented areas remained for six or more months. Any discolored area 5 mm. or more in diameter remaining after sixty hours was considered a positive reaction. The severity of the reaction did not seem to have any bearing on the serum titer, but did vary closely with the degree of sensitivity as shown by the clinical findings and reaction to therapeutic antigen. The intradermal reaction is a valuable guide in determining the proper dosage of therapeutic antigen.

The positive intramuscular test is determined by a rise in temperature to 100°F. or more during the forty-eight-hour period following the intramuscular injection of 0.5 cc. of antigen solution. The material used was equivalent to 2,500,000 bacteria per cubic centimeter. The normal person shows no rise in temperature when many times the indicated dose is injected. It is unusual to find a noninfected person showing more than the slightest rise in temperature after the intramuscular injection of as much as 1 cc. of the commercial vaccine, concentrated to contain 2,000,000,000 bacteria per cubic centimeter.

Agglutination tests were carried out before any antigen was used intradermally or intramuscularly. It was found that intradermal tests made with the dilute antigen did not appreciably increase the serum titer. Strong concentrations of antigen and strong suspensions of the vaccine increase the titer somewhat, but for a period of only a few weeks. The titer is influenced by intramuscular tests, particularly if a strong antigen solution or heavy vaccine suspensions are used. The intramuscular test was depended on mainly when the agreement of the other tests was open to question. It always agreed with a negative intradermal test. In our hands the intramuscular test proved

very valuable, but the reactions sometimes induced were disturbing to the patient.

By this method of investigation any patient presenting clinical evidence as well as showing two positive tests of the three available was considered to have chronic brucellosis. Certain complaints and physical findings were always present, or had recently been present, in all cases showing the required positive laboratory tests.

Of our 441 positive cases, more than 50 per cent have been under observation for from two months to four and a half years. About 90 per cent of these patients followed the advised treatment. Less than 10 per cent either have been living at a distance or refused to believe that such a condition existed. This disbelief seems to arise from a dearth of available information on this subject.

Conclusions

We believe that chronic brucellosis is prevalent in southern New England. It is of economic importance because it is often a cause of disability sufficient to prevent normal physical activity among working people.

Many so-called neurasthenics are suffering from this condition. Its clinical aspect is varied, and puzzling to the patient and physician alike. It does not follow the usual course of chronic infection so much as it does that of a chronic allergic state. If we consider this condition from a standpoint of allergy, a more reasonable system of treatment would be desensitization.

Practical, simple and quite reliable methods of diagnosis are available and should be more generally utilized.

The general incrimination of raw milk as the chief source of brucellosis is subject to criticism, as the contamination through other food products and through other channels is of equal importance.

A plea is entered for more serious consideration of the victims of chronic brucellosis and for a more careful study of the disease.

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REPORT ON MEDICAL PROGRESS

ALLERGIC DISEASES

With Special Reference to Histamine and Acetylcholine

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WHY should histamine be regarded as the active end substance which results from many kinds of reactions and is, therefore, the immediate cause of asthma? The question was asked in the review[1] of last year, and demands a more detailed answer than the one there given.

In 1910, Barger and Dale[2] studied the poisons of ergot, and isolated beta iminazolylethylamine as one of them. They called it "histamine." They showed that histamine could cause contraction of the isolated uterus of the guinea pig when added to the bath in which the strip was suspended, and a marked fall in the cat's blood pressure when injected intravenously into the intact animal. These two effects are so characteristic that they are used today as measures of the concentration of histamine in unknown solutions. When histamine in tiny doses is injected intravenously into a guinea pig, severe bronchospasm develops at once, and the animal usually succumbs with signs and symptoms which are quite like those of anaphylactic shock. When histamine, even in high dilution, is applied to a scratch in the skin of animals and man, an immediate reaction with urticarial wheal and surrounding erythema develops within a few minutes.

On the basis of its physiologic effects, there is ample reason to suspect histamine as the ultimate active agent in anaphylactic and allergic reactions, and the theory that the substance is released from normal cells following injury by trauma or by a specific antigen-antibody reaction taking place in the cell surface is not unreasonable. However, as Best and McHenry[3] ask, "Can such a potent substance be present in the active state in living tissue, and if so, what holds it in its place?" It is easy to show that extracts of many different tissues, as well as of such substances as ergot, yeast, peptone, casein and pituitary extract, have a depressor action on the cat's blood pressure or stimulate the guinea pig's intestinal strip, but it is not so easy to be sure that the activity of the extract depends on histamine. Fortunately it has been possible in many cases to identify the histamine by chemical means as the picrate. The first identification was the isolation of histamine from intestinal mucosa by Barger and Dale[4] in 1911. Some years later, Abel and Kubota[5] isolated histamine dipicrate from dried pituitary material, and so claimed that the uterus-stimulating factor in pituitary extract was nothing more or less than histamine. Now, however, it is recognized that pituitrin has a more specific action that does not include the flush, the low blood pressure and the vasodilatation produced by histamine.

Meantime, it was known from chemical studies that histidine is largely distributed through the body, and that histamine could be made from it by processes of oxidation as well as by the action of bacteria. This last possibility made it necessary to study tissues that were fresh and uncontaminated. It was not until 1927 that Best, Dale, Dudley and Thorpe[6] prepared histamine in crystalline form from the normal liver, lung, spleen and muscle of the ox.

The properties of histamine are interesting. It is very poisonous; the quantities needed to kill by intravenous injection are extremely small, although the lethal dose varies among different animals. The guinea pig is killed by 0.30 mg. per kilogram of body weight, while the rat is much more resistant, requiring 300 mg. per kilogram for a fatal result. Weiss, Robb and Blumgart[7] used the facial flush (capillary dilatation) that follows the intravenous injection of histamine into man as a measure of the velocity of blood flow, and found that the safe intravenous dose for man was not larger than 0.001 mg. per kilogram of body weight, or an average total dose of 0.07 mg. Actually the authors gave 0.35 cc. of a 1:5000 dilution of ergamine acid phosphate. Pertinent here was their observation that all patients with emphysema, bronchitis and asthma showed temporarily increased dyspnea with the symptom, asthma, after the administration of histamine. The patients were susceptible to the drug. Furthermore, it is known that normal persons and also asthmatic patients regularly show an immediate local reaction when a drop of 1:10,000 dilution (about 0.02 mg.) of histamine is applied to a scratch in the skin.

Histamine is stable. The method of assay, as modified by Code,[8] begins with the removal of protein substances by boiling in the presence of

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acetic acid; the histamine remains intact in the filtrate. In this regard, histamine behaves very differently from acetylcholine.

A second constituent of normal tissues is acetylcholine. A review of this substance, including its relation to other tissue derivatives, is included in the recent book by Cannon and Rosenblueth,[9] *Autonomic Neuroeffector Systems*. In 1906, Hunt and Taveau[10] published a paper "On the Physiological Action of Certain Choline Derivatives and New Methods for Detecting Choline." They pointed out that the acetic ester of choline was extremely active as a vasodilator and depressor substance. Later, Dale[11] found that aside from histamine, ergot contained another very active substance, the injection of which could slow the heart rate, cause marked vasodilation and stimulate contractions of the gastrointestinal tract; the substance resembled acetylcholine. In 1921, Loewi[12] isolated the hearts of two frogs and filled them with Ringer's solution. The vagus of one was stimulated for a few minutes. The fluid in that heart was then transferred to the second heart, which thereupon reacted as if its own vagus had been stimulated. The first vagus stimulation had given rise to a chemical substance that Loewi thereupon called *Vagusstoff*. After this, other investigators found that stimulation of the parasympathetic nerves running to many different organs — the chorda tympani nerve to the salivary gland, for example — caused the appearance of a similar substance in the blood, and that this could be carried to other organs, to mimic in them the effects of parasympathetic nerve impulses. The *Vagusstoff* was identified later as acetylcholine.

Acetylcholine has two pharmacologic characteristics that distinguish it from histamine. The base choline is stabile, but it is not very active physiologically. Its esters, on the other hand, are labile but they are many hundred times as active as the base choline, and it is acetylcholine which has been identified in the body cells under certain conditions and which has been studied so extensively. However, when acetylcholine is introduced artificially into the body it is destroyed almost at once on contact with animal blood or tissue. This destruction depends on an enzyme — cholinesterase — which is present in normal tissues and which acts by hydrolyzing the ester into its two original components. Loewi[13] and others showed that this enzyme could be inactivated by heat as are other enzymes. More important, the action of the enzyme is inhibited by the drug, eserine (physostigmine), as Loewi and Navratil[14] were able to demonstrate, and this protection of acetylcholine has played an important role in many studies. The action of eserine consists in preventing the union between acetylcholine and cholinesterase. Animals and tissues that are under the influence of eserine allow the full effect of acetylcholine to be exhibited and analyzed.

The second characteristic of acetylcholine is that its action is promptly and effectively prevented by atropine. Atropine appears to stop the access of acetylcholine to the cells of smooth and cardiac muscle and of glands. In spite of the fact that acetylcholine has a normal physiological function, it may (like histamine) become a poison when injected into man and animals. In the form of a stable synthetic compound — acetyl beta methylcholine — it has been used in the treatment of man and animals with profound effects. It causes contraction of striated muscles; it slows the heart and it lowers the blood pressure by causing a dilatation of peripheral arterioles; it causes sweating, flushing and rhinorrhea; finally, it may induce bronchospasm. All these effects are quite comparable with those following the injection of histamine. Each of the substances can induce asthma in susceptible persons. The one great difference is, however, that the effects of acetyl beta methylcholine can be blocked promptly by the administration of atropine, just as they can be enhanced by treatment with physostigmine; yet neither physostigmine nor atropine has any effect on the action of histamine. The importance of this relation is shown by the following report. Kokas, Sarkady and Went[15] sensitized dogs to foreign protein and then before the second shocking dose was given, they treated the animals with full doses of atropine. The fact that anaphylactic shock resulted as usual from the second dose and that atropine had not blocked the reaction was, to the authors, a demonstration that the anaphylactic poison was histamine and not acetylcholine.

These previous findings are summarized here for two reasons. First, there is today among students of the allergic diseases an increasing interest in histamine, even though as yet its role cannot be demonstrated with any assurance. Second, acetylcholine, like histamine, is found as a constituent of normal tissues, from which it is released by simple mechanisms, and it has effects that are much like those of histamine. It seems quite proper to examine the possibility that this other chemical neuroeffector — acetylcholine — may be playing a significant part in these peculiar clinical conditions.

The synthetic compound acetyl beta methylcholine (Mecholyl) is stable and has been used in many experiments both on man and on animals. Villaret and his co-workers[16] found that a dose of

20 to 40 mg. injected subcutaneously was enough to produce an attack of asthma in each of fifteen asthmatic patients and quite regardless of the type of asthma from which the individual patient suffered. Starr, Elsom, Reisinger and Richards[17] and their associates have studied the clinical effects of acetyl beta methylcholine on many patients with various conditions including, especially, paroxysmal tachycardia (to use the parasympathetic effect on the pulse rate) and Buerger's disease (to use the peripheral vasodilator effect). Included in their study is the observation of a young man with a previous history of asthma who developed a typical asthmatic attack immediately following the administration of the drug. The attack lasted for about three minutes and then subsided spontaneously. The dose is not stated.

Fraser[18] has studied the clinical effects of acetyl beta methylcholine extensively. Among other experiments, he watched under the fluoroscope the introduction of Lipiodol into the trachea and bronchi of a woman who had just been given a dose of 25 mg. of Mecholyl intramuscularly. A definite constriction of the smaller bronchi was observed.

Myerson[19] and his associates have also worked with the same drug but so far their subjects have not included patients with asthma.

Parrot[20] gave a milligram of eserine salicylate to a group of fasting individuals, drew samples of blood and then tested them on eserinized leech muscle. Using the blood of normal persons, no contraction occurred,—no acetylcholine could be demonstrated,—but in the blood of asthmatics, acetylcholine was found in seven out of the eight samples studied.

An analogous experiment but performed on rabbits is reported by Wenner and Buhrmester.[21] These authors sensitized rabbits to egg white and bled them during the shock resulting from a later dose. The acetylcholine content of the extracted blood was tested by intravenous injection into atropinized cats, so as to exclude the effect of histamine, and was then applied to a strip of eserinized muscle from the back of a leech. It was found that the amount of acetylcholine in the blood of the shocked animals was equivalent to a 1:1,000,000 or 1:10,000,000 dilution of acetylcholine chloride, whereas the blood of other sensitized but unshocked animals was equivalent to about half that strength, and the blood of normal nonsensitized animals contained no measurable amount. This result is especially interesting because the original sensitized rabbits were not treated with eserine before the shock and so one can assume that if acetylcholine was produced by the shock, the amount destroyed before the blood was drawn was larger than the amount estimated by the test.

Milhorat[22] made a different approach to the problem. He studied the cholinesterase activity of the blood in 109 patients with various diseases. He added the serum to known quantities of acetylcholine, and considered the amount of acetic acid set free by the enzyme as representing the amount of acetylcholine in the specimen. Five patients with asthma were included but the results, as in the other cases, varied widely and no conclusions could be drawn.

So far there is no other report of studies on the blood content of acetylcholine in patients with asthma. The problem is difficult, partly because the quantities to be expected are infinitesimal, and more important, because this substance in contrast to histamine is very delicate and labile. Obviously, however, further studies must be made because theoretically, as Alexander[23] said in his discussion of Wenner and Buhrmester's paper, histamine does not quite fill the bill but acetylcholine does,—and I add,—except for the one fact that its effect on the cells is easily blocked by atropine.

On histamine, recent studies include the following. If histamine is responsible for such a condition as status asthmaticus, an increase of histamine in the circulating blood might be anticipated. Riesser[24] tried to find it, but could demonstrate no more histamine in the blood of asthmatic patients than in that of tuberculous patients. Randolph[25] studied the blood of several patients with severe asthma, in 2 cases within a few hours of death from the disease, but the values obtained were within the limits of those found for the blood of normal persons and for the blood of other asthmatic patients between attacks. Fiessinger, Gajdos and Panayotopoulos[26] studied the blood histamine in various diseases. Using the color reaction of Pauly, which is even less accurate than the biological test, they showed slightly more histamine in the blood of patients with urticaria and asthma than in that of those with cirrhosis of the liver. Code and Hester[27] examined the blood of 2 horses and 6 calves during anaphylactic shock and found the quantity of histamine low rather than high. In a similar experiment on dogs, Dragstedt and Mead[28] found that the histamine in lymph and blood varies directly with the degree of shock, and disappears as the shock subsides. Such studies are difficult because the method of determining histamine, originally devised by Barsoum and Gaddum[29] and modified by Code,[30] consists in comparing the response of an intestinal strip from a guinea pig to the unknown solution with its response to a histamine solution of standard strength, and because the values obtained are less

than 1 gamma (a thousandth of a milligram). Code has shown that 90 per cent of the blood histamine is in the white cells and particularly in the eosinophilic leukocytes. Katz[31] observed that the leukocytes can release histamine. He immunized rabbits to egg white and added small amounts of this substance to their blood in vitro, incubating the mixture for ten minutes. When the sensitized blood had undergone "shock," its content in histamine was from one to six times as high as in the control blood drawn and incubated without the addition of egg white.

Meantime, Rose and Browne[32] have sought to find why it is that the rat is many times as resistant to histamine as is the guinea pig. (I should like to think of patients with asthma as behaving toward histamine like guinea pigs, while normal persons behave like rats.) Rose and Browne injected a generous dose intravenously into a series of rats, and killed the animals at intervals in order to study their organs. They found that the injected histamine collected rapidly (within fifteen minutes) in the kidneys, from which it was redistributed slowly to the other tissues. If adrenalectomized animals were used, the rate of redistribution was much slower in accord with the general decrease in resistance of the animal. Perla[33] observed that if sterile saline solution is injected intraperitoneally into rats, or if they are fed salt for several days before the dose of histamine, their resistance to the latter is increased. One would like to correlate this finding with the favorable effect that often follows the intravenous injection of normal salt solution into patients with asthma.

There have been one or two attempts to apply the histamine theory of allergy to practical use. In 1935, Dzsinich[34] treated a group of asthmatic patients with injections of histamine every other day, hoping to change their allergic susceptibility (*Bereitschaft*), and claimed that 12 out of 15 patients obtained complete relief. The duration of relief and the types of cases treated are not described. I have tried the method on a few patients with asthma, but with no striking results. Incidentally it was impossible for me to increase the subcutaneous doses above the certain small quantity that produced each time a mild flushing of the skin and a definite increase of the wheeze. The tolerance for histamine could not be increased, at least by this method. Farmer[35] has recently tested the theory of desensitization by histamine by treating animals. Guinea pigs were sensitized to horse serum and then treated with histamine injected intraperitoneally at intervals of one to three days for a period of twelve to eighteen days. Later the uterine strips were suspended in the Dale bath and tested with increasing doses of horse serum. Farmer found that the strip from the histamine-treated animals — both sensitized and normal — required larger concentrations of horse serum to produce contraction than did the strips from the animals not treated with histamine. In another paper, Farmer[36] reports that the feeding of histamine by mouth could also diminish the reaction of the sensitized uterine strip.

"Histaminase" has a current vogue. In 1930, Best and McHenry[37] tried to discover why the effects of histamine, whether injected intravenously or subcutaneously, were so transient. From normal dogs, they took 20-gm. samples of various tissues and suspended each in 100 cc. of salt solution, adjusting the mixture to pH 7. Two samples of each kind of tissue were studied. Forty milligrams of histamine was added to one sample without other treatment, and to the other after boiling. The pairs were incubated at 37°C. for seventy-two hours, after which histamine determinations showed 36 mg. still present in the heated material, but only 0.3 mg. in the unheated. This experiment demonstrated that 20 gm. of moist tissue — in this case, kidney — could destroy almost 40 mg. of histamine. Later a stable powder containing the histaminase was made by extracting fresh tissue with acetone and ether and rapidly drying the residue before a fan. They found that under favorable conditions, 200 mg. of powder will inactivate 2 mg. of histamine in twenty-four hours. However, the activity varies for different organs, the kidney and the intestine showing activities many times as great as those of other organs. Clinical interest in histaminase has been aroused by the report of Foshay and Hagebusch[38] that histaminase given by mouth in the form of tablets each containing 5 "histamine-detoxicating" units (three to fifteen tablets a day) or intramuscularly in ampules each containing 1 unit (up to four ampules a day) relieves serum disease.

Laymon and Cumming[39] treated 17 cases of urticaria with the tablets and claimed a cure in 10. In atopic dermatitis, however, no beneficial results were obtained in 8 cases. To interpret such findings is difficult. The clinical conditions are always extremely variable, and hard to control.

Experimenting on guinea pigs, Karady and Browne[40] used the ampules containing histaminase, injecting the contents intravenously fifteen minutes before an otherwise fatal intra-abdominal dose of histamine. The animals survived. Furthermore, similar treatment protected them against anaphylactic shock. That these results did not depend on some nonspecific effect of the alarm reaction in guinea pigs, as described by the same authors,[41] is attested by the fact that when the histaminase was inactivated at 56°C. for an hour

before being injected all its protective power was lost. As the authors comment, the time element in these experiments is important. In the test tube, destruction of histamine by the ferment requires between forty-eight and seventy-two hours, as Best and McHenry[37] showed. In the living animal, however, protection occurs in a few minutes. In my laboratory, the fresh organs of rats and of guinea pigs have been ground finely and let stand for periods of several minutes to several hours in salt solution containing various small concentrations of histamine, but so far no evidence of neutralization has been obtained when the mixtures are tested on the human skin and the reaction is compared with that of control solutions.

The discrepancy between the experiments made in the test tube and those made in the living animal is hard to explain. Still other observations are hard to fit into the picture as a whole. By the proper use of a galvanic current Abramson and Ochs[42] were able to drive histamine into the intact skin so that an immediate wheal resulted by electrophoresis. Then Abramson and Engel[43] found that by reversing the polarity the histamine could be drawn out and identified by reintroduction into a new area of skin. Later the method was applied to skin tests with ragweed pollen in sensitive patients. By electrophoresis typical allergic wheals could be produced, but no histamine could be drawn out when the poles were changed. In preliminary experiments, Sulzberger[44] has mixed the enzyme histaminase with histamine and with various allergens, testing the mixtures on the skin of his sensitive patients, but so far he has been unable to demonstrate any neutralization — in the test tube.

Discussion

There is evidence that histamine and acetylcholine may each be concerned with clinical allergy. So far, however, this evidence consists chiefly in the striking effects that occur when these substances are injected into animals and man. Each substance is quite capable of producing a clinical picture comparable to what is recognized as asthma, and further, each can be identified as a constituent of normal tissue. It is not surprising that there has developed a theory that one or the other is the end product resulting from the activity of a wide variety of exciting causes.

The method by which these two intracellular substances are released is interesting. Histamine appears after mechanical or toxic injury to the surface of the cell. Acetylcholine results from stimulation of the cell by nerves. The pathologic picture of asthma depends on the overactivity of the bronchial glands which pour out the mucoid secretion which gives rise to the intrabronchial plugs of tough rubbery consistence so common in asthma. If this were a nervous effect would one not expect other evidence of cholinergic activity in the body as a whole? Slow pulse, low blood pressure, diarrhea, colitis and perhaps peptic ulcer are not common in asthma, and the evidence of cholinergic activity is slight. The theory of direct injury to the bronchial wall by the allergic reaction resulting from the inhalation of the specific dust substance is more tenable, but one must also explain the development of asthma after the ingestion of specific foods or the subcutaneous injection of foreign substances which can reach the bronchi only through the blood stream. This, however, is possible and on the whole the theory of the release of histamine by injury is more acceptable than the release of acetylcholine by nerve stimulation. Moreover, the lack of relief of asthma by atropine helps to exclude acetylcholine.

Whether one must assume that the patient with asthma behaves toward either acetylcholine or histamine in a manner different from the normal person is a proper question. That the substances increase in the blood during anaphylactic shock or during an attack of asthma is suggested by some experiments but not by all. A more probable explanation is that the patient with asthma reacts to similar quantities in a manner different from the normal person, and it is possible that an approach to this theory will be found later. The suggestion that histaminase may be effective in the treatment of asthma and allied conditions requires much more study, and one must not overlook the apparent vast difference in the time factor between neutralization in vitro and in vivo. In treatment, histaminase needs much wider trial before one can say that it is of value. Serum disease, hives, asthma and hay fever are prone to occur in attacks which may come and go suddenly. The cause of the attack as well as the cause of the recovery from it may, in a given case, depend on any one of a number of possible factors. The situation is always complicated, and observations in these diseases are always hard to control. New observations must be made, but their results must be interpreted with the greatest caution.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

ANTEMORTEM AND POSTMORTEM RECORDS AS USED IN WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

CASE 26161

PRESENTATION OF CASE

A twenty-five-year-old unemployed single man entered the hospital complaining of "soreness" in both sides of the abdomen for the previous five days.

Ten years before admission he was told at another hospital that his spleen was enlarged and he was advised to have it removed. His father would not consent to this. He had visited the Out Patient Department of this hospital for some incidental complaint that he did not remember. Since that time he had noticed pigmented spots on his legs, which he attributed to mosquito bites. Five years before admission the family noticed that his abdomen was becoming progressively larger. At the same time the patient noticed that the gums bled easily when he brushed his teeth or when he had teeth extracted. The tendency had improved in recent years. About a year before admission the color of the skin became darker, especially over the face. Five months before admission the right ankle became swollen and tender, without preceding trauma. X-ray films were negative. The ankle remained swollen and tender for about a month. Two and a half months before admission he had worked on a PWA project for two weeks, clearing brush, but this had to be discontinued because the ankle bothered him. He again went to the local hospital, and four more x-ray films were taken, which were negative. Since then he had remained in his room and had done no further work. The ankle improved in about two weeks. Three and a half weeks before admission he again visited the hospital because of recurrence of swelling in the right ankle. He stayed there a week and was told that his teeth were bad. Two and a half weeks before admission he had a premolar tooth extracted. Following this the gum bled for two days. Three days following the extraction, nodes in the right side of the neck became swollen and his throat became sore. The throat improved in the course of a week or ten days. Four days before admission he noticed that he was becoming short of breath. He had vomited occasionally for several weeks; this became almost a daily occurrence. The abdomen had been a little sensitive for some months on the left side, but a few days before entry had been exquisitely tender on both sides.

His mother had been born in Nova Scotia, and his father in Massachusetts. They and six siblings were living and well.

The patient had been born in Massachusetts and had always lived there. He had had mumps, whooping cough and chicken pox as a child. Sixteen years before admission he had fallen from a tree and was unconscious for two or three hours, but suffered no aftereffects. The tonsils and adenoids had been removed sixteen years before admission; he had bled quite a bit following the operation.

Physical examination showed a thin, fairly well-developed, acutely ill man, with a copper-colored face. The voice was moderately high pitched and childish. The skin was dry and loose, and there were brown-black, slightly depressed areas of pigmentation over the anterior surfaces of the lower extremities below the knees. The teeth were partly missing, and those remaining showed caries and pyorrhea. There were small wedge-shaped fatty deposits in the sclera of each eye on both sides of the cornea. He had a thin beard over his chin but no hair elsewhere on his face. The hair on the head and in the axillary and pubic regions seemed normal. There was slight generalized adenopathy, but no nodes measured over 1 cm. in diameter. There were flatness and absent sounds below the third rib on the left and the fourth on the right anteriorly. Posteriorly there was flatness below the angles of the scapulas on both sides. The abdomen was very tensely held and was quite tender, especially over the left half. By percussion and palpation a mass occupying the left two thirds of the abdomen could be rather indefinitely outlined. On rectal examination a large smooth mass was felt outside the bowel rather high up. The blood pressure was 120 systolic, 70 diastolic.

The temperature was 102°F., the pulse 110, and the respirations 25.

The urine showed the slightest possible trace to a large trace of albumin on several examinations, with occasional white blood cells and occasional hyaline and rare granular casts. The stools were negative for gross and occult blood and did not show fat on staining with sudan III, both before and after acidifying and heating with acetic acid. The red-cell count was 3,600,000 at entrance and gradually fell to 2,500,000. The hemoglobin was 55 per cent (Tallqvist) at entrance and fell to 45. There were from 70 to 95 per cent polymorphonuclears on many occasions, and the white-cell count varied from 22,000 at entrance to 3600. An occasional myelocyte was seen in the smear. The red blood cells showed some variation in size

and shape and slight achromia. Platelets were normal in number at entrance but became somewhat diminished several weeks later. The oxygen capacity of the blood was 7.72 vol. per cent, the color index 0.80, and the volume index 0.86. There was no significant difference in the white-cell and differential counts before and twenty minutes after the administration of 0.5 cc. of adrenalin subcutaneously. The Hinton test was negative. The icteric index was 6, and the van den Bergh normal. The liver function showed 0 to 5 per cent retention in thirty minutes by the bromsulfalein test. The nonprotein nitrogen was 23 mg. per 100 cc. The phenolsulfonephthalein test of renal function showed 30 per cent excretion of dye in thirty minutes. The blood cholesterol was 42 and 61 mg. per 100 cc. at two determinations. The bleeding time was four minutes, and the clotting time twelve minutes, as determined in an 8-mm. test tube. The Congo red test for amyloid disease was negative. The fasting blood sugar was 91 mg. per 100 cc., the serum calcium 8.31 mg., the phosphorus 4.10 mg., and the serum protein 6.1 gm. No Bence-Jones protein was found in the urine. The total fatty acids of the blood were 280 mg. per 100 cc., an essentially normal figure.

An x-ray film of the chest was negative except for the presence of an exceedingly high diaphragm — at the level of the third ribs anteriorly and the level of the angles of the scapulas posteriorly. The bones of the skull, arms, pelvis and femur showed no definite variation from normal when examined three days after entrance. The plates of the right ankle were reported as negative. A flat abdominal plate showed generally increased density with obliteration of the normal soft-tissue shadows. An intravenous pyelogram showed that the left kidney was about twice the size of the right, but this was interpreted as being due to a congenital anomaly. There was no evidence of tumor. The epiphyseal lines along both iliac crests were open. A barium enema showed a low splenic flexure but no other definite abnormality.

During his stay in the hospital he continued to run an irregularly febrile course, the temperature varying from 98 to 103°F. His weight was 102 pounds at entrance, but this gradually fell to 94 in the course of several weeks. He remained quite ill and was always tender in the left upper quadrant, although this varied in degree from day to day. He vomited about once every two days, often in the morning after breakfast. A bone-marrow biopsy from the left tibia showed several focal areas of very active marrow with all the normal elements present; red-blood-cell formation was very active. About one month after entry he was given a short course of x-ray treatment (600 r, divided into three treatments of 200 r each) over the spleen; this was followed by some improvement, the size of the abdomen definitely decreasing.

During the latter part of his stay he had transient ankle edema, lasting a few days and then clearing spontaneously. He vomited more frequently during the last few weeks in the hospital. During that time it was noted on several occasions that the abdomen was quite tympanitic high in the left upper quadrant, a condition not present on admission. Five days before death, under local anesthesia, a small abdominal incision was made. Dense adhesions between the peritoneum and an underlying mass were found, and there was considerable bleeding encountered on separating these. A small V-shaped section of the underlying mass was removed, and the wound closed without drainage. Following this he continued to fail and died two and a half months after entry.

Differential Diagnosis

Dr. Siegfried J. Thannhauser*: I should like to give the following summary of the symptoms of this twenty-five-year-old man. He had been in another hospital ten years previously and since then had been continually ill and under treatment for numerous complaints of indefinite origin. Moreover, it must be believed that he was really a sick person during this period, because his physical development was not up to par and his secondary sex characteristics did not develop fully — his voice was high pitched and childish, a thin beard covered his chin, but there was no hair on any other part of his face. This kind of infantilism and sexual retardation usually indicates the gradual progression of a severe disease which, like an enemy from within, retards development.

An enlarged spleen had been observed ten years before when the patient was in the other hospital. I think there is no reason to doubt this statement, even though there is no definite mention of an enlarged spleen in the physical findings reported during the period of hospitalization here. However, the report did state that his abdomen was very tensely held and quite tender over the left half. The patient himself reported that for some months before his admission to the hospital, his abdomen had been sensitive on the left side and, later, on both sides. He vomited almost every day for a few weeks. A mass occupying the left two thirds of the abdomen could be rather indefinitely outlined by percussion and palpation.

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This mass was also felt by rectal examination; it was outside the bowel and rather high up. The flat abdominal x-ray plate showed a generally increased density, with obliteration of the normal soft-tissue shadows. There is no statement of an enlarged spleen. However, it is stated one month after entrance that the patient was given a short course of x-ray treatments over the spleen and that the size of the abdomen definitely decreased. But it must be re-emphasized that the history contains no exact statement about the spleen. I should nevertheless like to depend on the observation made ten years ago. Yet, something else must have developed in the patient's abdomen in addition to the enlarged spleen, because five years before admission the family had noticed that his abdomen was becoming progressively larger. The enormous mass noted in the physical findings was indefinitely outlined. The spleen alone, on the other hand, would always have very definite outlines. The smooth mass felt by rectum was certainly not the spleen, because, if so, it would not have been smooth. The intravenous pyelogram was evidently carried out to discover what other organs were involved in the large mass. It was found that the left kidney was about twice the size of the right, but this was interpreted as being of congenital origin. There was no evidence of a renal tumor. The barium enema also did not reveal a tumor, but only a low splenic flexure. In summary, I should like to say that all the search revealed nothing more than did the palpation, that is, the presence of an enormous mass with indefinite outlines. There is no statement of whether the mass moved with respiration. I should nevertheless like to assume that the mass did not belong to the kidney or to the intestines, but rather to the spleen and additional conglomerates probably present in the mesentery.

At the time when his spleen was pronounced enlarged at the first hospital, the patient also noticed pigmented spots, which persisted after their appearance. He attributed these to mosquito bites. Following up this symptom of pigmentation through the course of the disease, we find that about a year before the patient's admission here the color of the skin had become darker, especially over the face. During hospitalization, brownish-black slightly depressed areas of pigmentation were observed over the anterior surfaces of the lower legs. Small wedge-shaped, fatty deposits were noticed in the scleras of both eyes. Later, the copper-like color of the face was mentioned. The skin itself was dry and loose. In summarizing these symptoms, we have to accept the presence of a definite pigmentation, which had been increasing since the beginning of the disease.

Third, the patient had noticed before his admission to the hospital a tendency toward bleeding. This had first been observed after a tonsillectomy, and later after brushing his teeth. It was again noticed after the extraction of a tooth. With the extraction of another tooth, the gum bled for two days. Physical examination on entry revealed that his gums were in poor condition, but no bleeding spots were found.

The patient also reported that once after a tooth extraction he had swollen nodes in the neck, especially on the right side. That he had at the beginning of his hospital admission generalized adenopathy is a very important statement. It was mentioned, however, that no node was over 1 cm. in diameter. There is no subsequent mention of the adenopathy; but I believe it did not disappear, for otherwise reference would have been made to it.

The fifth feature that the patient himself had observed before admission to the hospital was swelling of the right ankle. The severe pain caused him to seek medical advice at different times; however, there were never any positive clinical or x-ray findings.

The patient's heart was normal. There were flatness and absent sounds below the third rib on the left and the fourth rib on the right anteriorly. There was flatness below the angles of the scapulas on both sides posteriorly. However, the x-ray film of the chest was negative, except for the presence of an exceedingly high diaphragm. There was no exudate, infiltrate or mediastinal shadow.

The patient did not mention that he had a fever before admission to the hospital. While at the hospital he had an irregularly febrile course, the temperature varying from 98 to 103°F. The pulse was about 110, and the respirations 25. He was very ill, and his weight fell from 102 to 94 pounds. The patient repeatedly vomited, very often in the morning.

Comparing the laboratory findings with the physical data, we note that the red-blood-cell count was 3,600,000; this gradually fell to 2,500,000. The hemoglobin dropped from 55 to 45. The white-blood-cell count varied from 22,000 to 3600. The polymorphonuclears were always 95 to 97 per cent; occasionally a myelocyte was seen.

Bone-marrow biopsy revealed an active marrow with normal elements. Despite the bleeding tendency, there was no infiltration of bone marrow with a tissue that did not physiologically belong there. X-ray study of all the bones did not reveal

any abnormality in shape or structure. There was also no sign of leukemia in the bone marrow.

Chemical examination of the blood revealed two things of importance: no bilirubin, and low cholesterol and fat levels. The fact that he did not have any bilirubin excludes an increase in hemolysis or blood destruction. The low cholesterol and fat contents should be evaluated, in my opinion, as a sign of progressive disease leading to cachexia.

The liver function test with bromsulfalein was normal. The phenolsulfonephthalein test of the renal function showed 30 per cent excretion in thirty minutes. There was also an adrenalin test, but there is no report that after the test the spleen decreased in size. There was only a note that the white blood cells did not differ, before and after.

I should like to discuss four possibilities for diagnosis: splenic-vein thrombosis, the so-called Banti syndrome; tumor of the adrenal gland or kidney, with invasion of the splenic vein and mesenteric metastasis; Gaucher's disease; and atypical abdominal Hodgkin's disease, with enlargement of the spleen and mesenteric lymph nodes, simulating a large tumor mass — probably reticulum-cell granuloma.

Splenic-Vein Thrombosis. When the patient was a youth, he had had an accident and later on developed a large spleen. While the platelets in thrombosis of the splenic vein are usually normal, the leukocytes are generally diminished in number. In this case there was leukocytosis, and only in the last few days a drop in leukocytes and platelets. The patient had never had ascites or signs of portal obstruction. The fever could be explained on the basis of the splenic-vein thrombosis, and the enlargement of the kidney and the presence of large amounts of albumin by a renal-vein thrombosis. However, neither the gradual development and presence of skin pigmentation nor the infantile physical appearance and retarded development are characteristic of splenic-vein thrombosis. Furthermore, the outstanding feature in the later development of splenic-vein thrombosis is ascites. No masses were felt in addition to the spleen.

Tumor of the Adrenal Gland or Kidney. In favor of this diagnosis is the fact that an enlargement of the left kidney was noted. However, the x-ray examiner himself did not agree to the diagnosis of a tumor of the kidney. In considering a tumor of the adrenal glands, I do not know of any such tumor leading to a definite pigmentation. Neither medullary nor cortical tumors have pigmentation as a symptom. The masses felt by the rectal examination could be produced by the metastasis of such a tumor. However, the occurrence of all the other features, such as the bleeding tendency, pigmentation and, especially, the ten-year duration of the disease, would be extremely rare in either renal or adrenal tumor. Even though nothing has been mentioned about the movement of the tumor with respiration, I should not like to believe that the kidney and spleen were confused in the examination made ten years before. Neither should I like to suggest that there was any confusion in the present examination.

Gaucher's Disease. The following three features are favorable for a diagnosis of Gaucher's disease: a large spleen and general adenopathy; a bleeding tendency; and skin pigmentation on the leg and face. However, against such a diagnosis are the following findings: a normal bone marrow; normal shape of the bones; no structural deformity of the bones; the presence of granulomatous tissue in the abdomen, as evidenced by the adhesions between the peritoneum and underlying masses that were noted at the time of the abdominal incision.

Hodgkin's Disease. After a discussion of these three possibilities, everything seems to draw our attention to a diagnosis of abdominal Hodgkin's disease. An initial symptom sometimes found in this disease is a tendency to bleed. An enlarged spleen is almost a constant finding. General adenopathy, which is present in Hodgkin's disease, was also observed in this case. Pigmentation of the skin and a dry skin are also found. I do not consider the pigmentation of the scleras of great importance. The intermittent fever in the last month of this case is also a feature of Hodgkin's disease. Leukocytosis in early stages but leukopenia and low platelets later are also observed. Objection may be taken to this diagnosis on the ground of the duration of the patient's illness, namely ten years. A duration of seventeen years has been observed, and I myself have a case under observation where the histological diagnosis was made ten years ago. The patient to whom I am referring is of about the same age as the one being discussed and shows exactly the same signs of infantilism. As a last indication of the granulomatous disease, I should like to call attention to the findings of the intra-abdominal biopsy, where adhesions between the peritoneum and underlying masses were found.

In conclusion, I should like to make a diagnosis of an atypical abdominal Hodgkin's disease of long duration, with pigmentation and, especially, involvement of the mesenteric nodes.

DR. FULLER ALBRIGHT: There are two or three clinical features which did not come out strongly in the history. The triangular areas of fat deposit in the eyes were very striking. We thought that they were typical of Gaucher's disease, and located

a picture in the literature that was identical. We also found very low blood cholesterol values in certain reported cases of Gaucher's disease. We thought that that was a point in favor of Gaucher's disease.

DR. THANNHAUSER: All cases of granuloma of long duration have low cholesterol values. I should not consider such values specific for Gaucher's disease.

DR. ALBRIGHT: We thought that these were so low that they were typical.

DR. THANNHAUSER: I should not like to make a diagnosis of Gaucher's disease without bone changes. I think that is almost impossible.

DR. ALBRIGHT: A good many cases in the literature do not have them, but the proof that they are true cases of Gaucher's disease may be lacking.

DR. THANNHAUSER: So you would think this to be a case of Gaucher's disease?

DR. ALBRIGHT: I do not remember how sure we were before the biopsy.

DR. TRACY B. MALLORY: I think you were much more certain after the biopsy. At the time of exploration very extensive abdominal adhesions were found and the surgeon with some difficulty cut through the peritoneum into a mass; he was unable to decide whether it was liver or spleen from which he took the biopsy. He thought it was spleen but was not certain even after he had finished the operation. The biopsy showed not only that it was spleen but also that it was filled with pale acidophilic foamy cells which were entirely characteristic of Gaucher's disease.

CLINICAL DIAGNOSIS

Gaucher's disease.

DR. THANNHAUSER'S DIAGNOSIS

Atypical Hodgkin's disease.

ANATOMICAL DIAGNOSES

Gaucher's disease, with involvement of the spleen, liver, adrenal glands and mesenteric lymph nodes.
Cirrhosis of liver.
Bronchopneumonia.
Organizing pneumonitis.
Hydrothorax, bilateral.
Perisplenitis, acute.
Bone-marrow hyperplasia.
Operative wound: splenic biopsy.

PATHOLOGICAL DISCUSSION

DR. MALLORY: At the time of autopsy both the liver and spleen were greatly enlarged, the liver weighing 2500 gm. and the spleen 2600 gm. It was the spleen that was felt by rectal examination. The liver, I think, helped to push it down that far. There was almost no room left in the abdominal cavity for the intestines and stomach. There was a diffuse adhesive peritonitis, which in a few places was still active enough to show some fresh fibrin; I think it must have been smoldering along for the entire period of abdominal tenderness. The biopsied specimen from the tibia, even when reviewed again after seeing that from the spleen, showed nothing to suggest Gaucher's disease. Half a dozen sections from the vertebrae at autopsy showed only scattered microscopic foci of lipoid-bearing cells. They were much too small and too infrequent to have produced any changes visible by x-ray. Numerous lymph nodes were involved, and there were extensive deposits, accompanied by considerable fibrosis, in the adrenal glands.

DR. ALFRED KRANES: Were there changes in the liver?

DR. MALLORY: The liver was unusual. It showed a definite fibrosis, and in the portal areas there were many Gaucher's cells. My impression was that it should be called a cirrhosis of the liver and that change was presumably due to these cellular deposits.

A PHYSICIAN: Was the large kidney congenital?

DR. MALLORY: Yes; it was slightly larger than the other one, but not markedly so.

DR. AUBREY O. HAMPTON: We looked at the x-ray films of the bones after the diagnosis had been made and again considered them normal.

DR. MALLORY: I think, Dr. Thannhauser, if we could have done a German autopsy we should have found more evidence of the disease in the bones.

DR. THANNHAUSER: But there were a few Gaucher cells?

DR. MALLORY: Yes.

A PHYSICIAN: Is it true that if you remove the spleen you get more bone lesions?

DR. THANNHAUSER: That is recorded in the literature, but there is no proof.

CASE 26162

PRESENTATION OF CASE

A sixty-five-year-old dog trainer was admitted to the hospital complaining of a "bloated" sensation in the abdomen of twenty-four hours' duration.

The patient had been well until eight years before admission when a series of operations were performed "at the same time" in an outside hospital for "ulcer, appendicitis and rupture." No more definite history about the illnesses which precipitated these surgical manipulations was elicited. He felt well after this time until about

twenty-four hours before admission, when he began to feel "bloated" and noticed increasing abdominal distention. He vomited all ingested food, and was repeatedly unable to retain doses of castor oil and Epsom salts, which he took in a vain effort to purge himself. He failed to obtain relief with enemas and passed nothing by rectum. He complained of abdominal discomfort but apparently of no real pain or nausea. There were no other symptoms.

Except for an attack of typhoid fever thirty years before admission, from which he recovered uneventfully, the remaining past history was negative.

The physical examination revealed a well-developed and nourished man in no acute distress. Examination of the heart and lungs was negative. The blood pressure was 130 systolic, 70 diastolic. The abdomen was distended and tympanitic. There was a diffuse, moderately acute tenderness over the entire abdomen, but no muscle spasm or palpable masses were noted. Auscultation revealed frequent high-pitched peristaltic rushes. Well-healed scars in both inguinal regions and in the right rectus muscle were present; they were non-tender, and no masses were palpated beneath them. The remaining physical examination, including rectal examination, was negative.

The temperature was 98°F., the pulse 112, and the respirations 22.

Examination of the blood revealed a red-cell count of 5,300,000, and a white-cell count of 20,000. The urine showed a specific gravity of 1.022, a + albumin test and a negative sugar test; the sediment contained innumerable white blood cells.

A flat abdominal x-ray plate revealed gas-filled loops of small intestine in the left abdomen.

On the day of admission an operation was performed.

Differential Diagnosis

Dr. George A. Marks: This is the history of a sixty-five-year-old man who had been in apparently excellent physical condition, without loss of weight or anything else to indicate progressive chronic disease, but with two isolated episodes of pain in the past history separated by an eight-year symptomless interval. Another outstanding item in the picture is the fact that although he was distended, to an unrecorded degree, he had had no real pain, and although he had vomited he said that he had had no nausea. The physical examination is rather non-localizing in that the tenderness mentioned was diffuse. The distention was general, and there was no muscle spasm or palpable mass.

I think on the basis of history and physical examination one is justified in ruling out such severe abdominal accidents as perforated ulcer, mesenteric thrombosis and fulminating acute pancreatitis, all of which might produce one or more of the symptoms he had on admission. The abdominal distention, although unaccompanied by pain, appears to have reached a fairly marked degree in twenty-four hours. The laboratory findings were definite. He had a slightly elevated red count and a definite leukocytosis. It is unusual to have a small-bowel obstruction from the commoner causes — adhesive bands and strangulation — progress to this degree without severer pain, provided there is complete obstruction. On the other hand, a progressive shutting off of the intestinal lumen might result in such a picture as this, although that is a little unlikely.

We can rule out large-bowel disease, particularly in view of the x-ray findings, the absence of lower abdominal symptoms and the negative rectal examination. There is another cause of abdominal distention to be considered here, namely one due to a lesion outside the gastrointestinal tract, notably in the kidney. Such distention is usually due to paralytic ileus, although it does not need to be. In line with a renal lesion is the urinary sediment with many white cells.

May we see the x-rays?

Dr. George W. Holmes: On the left side of the abdomen there are moderately dilated loops of bowel containing gas, which I should interpret as being small bowel. There is a considerable amount of fecal material. It does not look as though the large bowel were dilated or contained gas. There is surprisingly little in the small bowel in view of the distention that is mentioned.

Dr. Marks: Do you see evidence of calculi in the kidney?

Dr. Holmes: I do not know that you would see them in these films. The amount of fecal material present would obscure a small stone; but if there were a good-sized stone you would see it. The diaphragm is in normal position.

Dr. Marks: We have nothing, then, to back up the suspicion of urinary-tract involvement, and it seems wisest to assume that the distention was due to an intrinsic lesion of the intestinal tract. It remains to be explained why this man had distention with so little pain and why the outstanding laboratory findings should be leukocytosis and a questionable increase in red cells. It seems to me that the thing which could most readily explain the whole picture is something that would allow progressive obstruction to occur, such as a foreign body in the intestinal tract. This man had had typhoid fever thirty years before, and this

fact furnishes a background for gall-bladder disease and allows a diagnosis of gallstone obstruction.

Another possibility is a gradually progressing volvulus which slowly shuts off venous circulation of an intestinal loop, without producing the severe pain of a sudden, complete obstruction. Such a lesion does produce a transudation of fluid in the abdominal cavity, with tenderness, and may result in a concentrated blood indicated by an elevation of the red-cell count; it may also be accompanied by a leukocytosis. The situation calls for a decision as to whether one is going to operate as well as make a diagnosis, thus bringing up the question as to whether the patient ought to be treated conservatively by suction or a Miller-Abbott tube. I think the leukocytosis is an indication of existing or impending interference with the circulation of the small bowel and forces a decision to operate rather than to attempt deflation. I should put a slowly progressive volvulus of the small intestine as my first choice, but I should not be surprised if, in view of the urinary findings, something outside of the intestinal tract was found as a cause of the distention.

DR. TRACY B. MALLORY: Dr. Thompson, you saw this man in the Emergency Ward?

DR. RICHARD H. THOMPSON: Yes. We believed that the findings were typical of acute small-bowel obstruction, and in view of the brief history and elevated white count, and the fact that the patient was in good condition, we decided to operate immediately. The first thing that I noted on exploring the abdomen, feeling in among dilated loops of small intestines, was a firm mass with a slightly rough surface which I thought might be a bolus of some kind in the bowel, but it soon became evident that it was a mass in the mesentery of the small intestine. There was no obstruction at the time the abdomen was opened, but there were two points in the jejunum which had undoubtedly been adherent to the mesenteric mass in such a way as to cause small-bowel obstruction by kinking. On the wall of the small intestine, which was supplied by the portion of mesentery in which the mass was found, were six or seven small firm nodules. Since I believed I was dealing with a tumor of the small intestine with metastases to the mesentery, the entire mass was resected. One or two nodules were noted distal to the resected mass. However, it seemed unwise to put the patient through a more extensive procedure, so an end-to-end closure was done and the abdomen closed.

CLINICAL DIAGNOSIS

Intestinal obstruction, acute.

DR. MARKS'S DIAGNOSIS

Progressive volvulus of small intestine.

ANATOMICAL DIAGNOSIS

Carcinoids, multiple, of the ileum, with regional metastasis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The resected loop of ileum showed a number of disk-like plaques in the mucosa or submucosa varying from 3 to 6 mm. in diameter. Some of them had extended through the muscularis to the serosa, but none actually reached the surface of the latter. There was no mucosal ulceration over any of them, and none of them were large enough to have produced any obstruction. The main tumor mass was, as Dr. Thompson said, in the mesentery and represented a metastasis in a mesenteric node. It measured about 4 cm. in diameter. These findings are very characteristic and could hardly result from anything except a so-called "carcinoid" tumor of the bowel.

Although carcinoids are rather uncommon tumors we have seen three within the last two months. The story is almost always the same, that of small-bowel obstruction due not to the primary tumor, which rarely reaches a diameter of over a centimeter, but to a mesenteric metastasis which results in adhesions or volvulus. It is also common to find multiple primary tumors, whereas the metastasis is apt to be single. Even with metastasis the prognosis is excellent, since, though local metastasis is common, generalized metastasis is extremely rare. We have one case, for instance, followed for twenty years after resection of a segment of ileum. At the operation metastatic nodes were noted deep in the mesentery. At the time of death from lobar pneumonia they were still present but the tumor had not extended any further throughout that period.

DR. WYMAN RICHARDSON: What is a carcinoid — an endothelial tumor?

DR. MALLORY: The pathognomonic feature from the histological point of view is that the tumor cells are argentaffin. That means that, if you stain them with a proper ammoniacal silver nitrate solution, black granules can be demonstrated in the cytoplasm. The adrenal medulla and various other tissues give this same staining reaction. Argentaffin cells are found normally throughout the intestinal mucosa from the stomach to the rectum. Tumors arising from them are uncommon, however, except in certain locations. The tumors occur most commonly in the appendix, where they rarely give rise even to local metastases. The next

commonest site is the ileum, where they are almost always invasive and frequently spread to the regional nodes. Cases with generalized metastases have been reported, but they are extremely rare.

DR. WALTER BAUER: What does the lesion look like microscopically?

DR. MALLORY: If you look at it with low power you might think of a basal-cell carcinoma of the skin. You see anastomosing cords of deeply basophilic cells, but the cells are quite small, not spindle shaped, and extremely uniform in size. Once in a while minute glandular spaces are formed, but glands are unusual. To the experienced eye the picture is unmistakable without any special staining technic. The architecture is that of carcinoma, but the uniform, small cells and the absence of mitotic activity or nuclear atypicality rule out carcinoma.

DR. JOHN D. STEWART: In light of the type of the lesion would you advise going back for the two nodules outside the field of operation?

DR. MALLORY: I should not at his age. I am quite sure he will die of something else.

A PHYSICIAN: Was the primary tumor single or multiple?

DR. MALLORY: I think there were several, separate primary tumors, any one of which could have given rise to metastases, but have no way of knowing. They all look quite invasive but otherwise nonmalignant.

DR. ARTHUR W. ALLEN: Did any of the nodules ulcerate the mucosa or were they all in the wall of the bowel?

DR. MALLORY: They were all in the submucosa. Even when they invade the mucosa they never ulcerate.

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ANNUAL MEETING OF THE MASSACHUSETTS MEDICAL SOCIETY

The scientific program for the annual meeting of the Massachusetts Medical Society has in past years been split up, for the most part, into meetings of the various sections. This method of presentation has had the disadvantage of not allowing for a co-ordination of broad topics as they relate to the general practitioner. To those responsible for the arrangements it seemed wise to present a unified and continuous program rather than a divided one, and this was so voted last autumn at a meeting of the section chairmen and secretaries and the Committee of Arrangements. That this should be a desirable change was predicted by the success of the combined clinical meetings that have been held during one day of the sessions for the past three years. It has the further advantage of allowing members in all specialties, some of which are not represented by sections, to take part.

In planning the program according to these ideas it has been possible to schedule what appears to be a sufficient amount of material in a two-day meeting. The annual dinner will take place on the evening of the first day, Tuesday, May 21, and will be followed by the Shattuck Lecture. The meeting will be finished late in the afternoon of the second day.

Tuesday morning will be devoted to a consideration of miscellaneous topics presented from the point of view of the surgeon, pathologist, obstetrician, internist, urologist and radiologist. On Tuesday afternoon there will be a symposium on respiratory-tract infections. This will include papers on the common cold, bronchiectasis, lung abscess and tuberculosis. Dr. Francis G. Blake, of New Haven, will present the latest views on the treatment of pneumonia. Wednesday morning is to be taken up by a symposium on syphilis, and in this, the Society is fortunate in having Dr. Thomas Parran, of the United States Public Health Service, as a participant. Wednesday afternoon will be devoted to a symposium on sulfanilamide and allied compounds; various aspects of the use of such drugs will be considered, with a summarizing discussion by Dr. Perrin H. Long, of Baltimore. There is to be discussion of most of the papers, but in each case this has been assigned. Owing to the number of papers to be presented, open discussion will not be possible.

Because the round-table discussions inaugurated last year by the Worcester committee were so successful, it has been decided to continue them, with modification. They are to be under the direction of the various sections and will be held at nearby hotels and the University Club from noon to 2:00 p.m. on the first day of the meeting. Five subjects will be taken up, and an opportunity will be given for informal discussion of each, to be led by an authority in each field. Each meeting will be preceded by a luncheon, and it will be necessary for the Committee of Arrangements to have a general idea of the number planning to attend. Therefore, the cards enclosed with the preliminary programs must be promptly returned.

In addition to the scientific program and the round-table discussions there will be a large number of scientific and commercial exhibits. The moving pictures were more popular last year than previously, presumably because a timetable of topics was published in advance; a similar schedule will be followed this year.

All in all the entire program is comprehensive and well co-ordinated and should offer wider opportunity than ever before for the members to learn and to discuss present trends and developments of medical knowledge.

GERIATRICS

THROUGHOUT the life cycle, the responses of the body to environmental and intrinsic factors are constantly changing. There are, however, two periods in particular during which the reactivity of tissues and organs differs considerably from what one may call the "average" responses. These are the years of infancy and childhood and those of old age. The behavior of the human organism during its early developmental period has been studied extensively, but the nature of the involutionary processes of old age has received relatively little scientific attention. Geriatrics as compared with pediatrics has been little cultivated.

The diseases and the behavior of the body in old age cannot be looked on as simple quantitative deviations from the norm. Just as many diseases of infancy and childhood are specific or essentially different from those of adults, so also are the diseases of the aged. Old age is characterized primarily by a reduced reserve of all organs and functions and by a generalized narrowing of the homeostatic adaptations. These changes alter the symptoms, signs and prognosis of diseases in this group, and in addition there are disorders specific to the old. Surgery in the aged also requires special consideration; and remarkable advances have been made recently in this branch of medicine. Finally, the altered response of senile persons to drugs and other therapeutic agents should be recognized by physicians.

Further progress in the care of the aged depends on extensive systematic investigation in the field of geriatrics. Canstadt (1839), Geist (1860), Charcot (1868), Schwalbe (1909) and Schlesinger (1914) have emphasized the importance of diseases of old age, and it is of interest that a modern textbook describing such diseases is now available.* Contributions such as the one that appears in this issue of the *Journal* represent much needed information.

As the result of the recent progress in public health, preventive medicine and pharmacotherapy, it is expected that the average duration of life will be further prolonged. This increase in the number of the aged places added responsibility on physicians to secure more comfort and better medical and surgical care for them. There seems little doubt that geriatrics will become an important branch of medicine!

*Müller-Deham, A.: *Die inneren Erkrankungen im Alter*. Wien: Julius Springer, 1937. 408 pp.

MEDICAL EPONYM

BRIGHT'S DISEASE

Richard Bright (1789–1858), lecturer on the practice of medicine and one of the physicians to Guy's Hospital, included in his *Reports of Medical Cases, Selected with a View of Illustrating the Symptoms and Cure of Diseases by a Reference to Morbid Anatomy* (London: Longman, Rees, Orme, Brown and Green, 1827) the results of his investigations of the pathologic conditions associated with albuminous urine. Their epoch-making character has served to attach his name permanently to the whole group of nonsurgical diseases of the kidney. The following quotation is taken from the introductory remarks of the author:

> The different diseases of the heart and of the lungs on which dropsy depends, and the various changes to which the liver is subject rendering it a cause of impediment to the circulation, are still open to much investigation. . . .
>
> There are other appearances to which I think too little attention has hitherto been paid. They are those evidences of organic change which occasionally present themselves in the structure of the KIDNEY; and which, whether they are to be considered as the cause of the dropsical effusion or as the consequence of some other disease, cannot be unimportant. Where those conditions of the kidney to which I allude have occurred, I have often found the dropsy connected with the secretion of albuminous urine, more or less coagulable on the application of heat. I have in general found that the liver has not in these cases betrayed any considerable marks of disease, either during life or on exami-

nation after death, though occasionally incipient disorganization of a peculiar kind has been traced in that organ. On the other hand, I have found that where the dropsy has depended on organic change in the liver, even in the most aggravated state of such change no diseased structure has generally been discovered in the kidneys, and the urine has not coagulated by heat. I have never yet examined the body of a patient dying with dropsy attended with coagulable urine in whom some obvious derangement was not discovered in the kidneys.

R. W. B.

OBITUARY

HERMAN FRANK VICKERY

1856 - 1940

The death of Dr. Herman F. Vickery must not pass without a tribute to the worth and importance of his life. For, although he retired many years ago, he played a prominent part in establishing the foundations upon which, in Boston, our present medical structure has developed.

He was born in Rochester, New York, in 1856. Graduating in 1878 from Harvard College and in 1882 from Harvard Medical School, he was a leader in scholarship and was highly regarded by his classmates for his earnestness and sincerity. He served with credit as a house pupil at the Massachusetts General Hospital, starting in 1882, and followed this with a year of study at the University of Leipzig and at the Vienna General Hospital. Returning to Boston in 1883 he entered on the practice of medicine, in which he continued until 1917; from 1884 onward he was identified with the work of the Massachusetts General Hospital and the clinical instruction at the Harvard Medical School.

The period of nearly four decades in which Dr. Vickery served was one in which medicine underwent a process of extraordinary development. During his internship, surgeons still operated in frock coats, medical therapeutics depended principally on empirical pharmacology, and laboratory diagnosis included little more than urinalysis. At the time of his retirement, medical procedure had assumed a general pattern essentially similar to that of today. In the interval, among other advances too numerous to mention, there were introduced the clinical applications of bacteriology in tuberculosis, diphtheria, typhoid fever, syphilis and other diseases, which revolutionized diagnosis and prophylaxis and, in some, treatment. Abdominal surgery, gaining impetus from the recognition of appendicitis, accomplished the major part of its impressive development. The x-ray machine, the sphygmomanometer and the electrocardiograph were invented, and technics developed. Clinical and experimental research added many new conceptions and led to the progressive evolution of the clinical laboratory. And it is to be remembered that, coincidentally with these advances, there were constantly appearing, in even greater volume, claims of discoveries which were not substantiated, so that it was only by a laborious process of proving the true and eliminating the false that sound progress was attained.

Throughout these decades, Dr. Vickery served the hospital faithfully and efficiently, advancing through the years in the responsibility of his position and in the esteem of his colleagues. While he was somewhat overshadowed by his two outstanding seniors, Dr. Reginald H. Fitz and Dr. Frederick C. Shattuck, his careful and painstaking approach together with his knowledge of medicine and his insight into human nature caused him to be recognized as an exceptional clinician. Although the requirements of his large private practice precluded original research, he exercised a most wholesome influence through a highly developed critical ability that enabled him to evaluate the publications of others with unusual accuracy, thus escaping the pitfalls of current fallacies while confirming and utilizing real advances. Through his long period of service to the hospital he demonstrated by example the value of clear vision and sound conservative judgment, and it was by these qualities more than by precept that he earned the enduring gratitude and appreciation of the long succession of interns who served under him. He also set a noteworthy standard by the meticulous performance of all his duties. If, as is often said, the Massachusetts General Hospital is outstanding for the conscientious thoroughness of its routine work, there is probably no one who did more to justify this reputation than did Dr. Vickery.

He was honored by election to the presidencies of the Boylston Medical Society, the Boston Society for Medical Improvement and the Suffolk District Medical Society, and to membership in the Association of American Physicians. He was associate editor of Sajous's *Annual and Cyclopedia of the Medical Sciences,* and to this he contributed articles, notably on rheumatic fever, chorea and rheumatic heart disease, containing original observations still credited with influencing our present conceptions. He published a translation of Strümpell's *Textbook of Medicine.* He was the first in this country to report cases of psittacosis. But, more than for his publications, he is to be remembered for the influence of his life of service in sustaining and consolidating medical progress.

F. W. P.

MASSACHUSETTS MEDICAL SOCIETY

SECTION OF OBSTETRICS AND GYNECOLOGY*

RAYMOND S. TITUS, M.D., *Secretary*
330 Dartmouth Street
Boston

PUERPERAL SEPSIS FOLLOWING NORMAL DELIVERY

Mrs. M., a thirty-eight-year-old para IV, about thirty-six weeks pregnant, entered the hospital on the afternoon of March 14, 1940; the membranes had ruptured twenty-four hours previously, and she was having indefinite contractions.

The family history was negative. The patient's past history included the usual children's diseases and diphtheria. The tonsils had been removed, and in 1929 a suspension and appendectomy had been performed. The three previous pregnancies and deliveries were uneventful; there was no history of miscarriage. Catamenia began at twelve and were regular, with a twenty-eight-day cycle. The last normal period was July 10, 1939, making the expected date of confinement April 17. The pregnancy had been normal and uneventful until the day of entry to the hospital.

Rectal examination at 7 p.m. showed the cervix to be three-fingers dilated and very soft. A normal delivery was effected at 7:30 p.m. The baby was a boy and seemed in good condition; he was not weighed. The placenta and membranes were delivered intact.

The following morning, twelve hours after delivery, the temperature was 99.6°F., and the pulse 110. Four hours later the temperature was normal, but in the afternoon, following a slight chill, the temperature rose to 103.2°F., with a pulse of 116. The temperature gradually fell during the night until it was again normal. At 9 a.m. the next day, March 16, following a slight chilly sensation, the temperature went to 102.0°F., and later in the day to 102.6. Physical examination showed a somewhat reddened throat and a slightly distended abdomen; the lochia was not remarkable. A consultation was immediately held with a surgical bacteriologist. Cultures were taken from the lochia, throat and blood stream, and all eventually showed hemolytic streptococci. Sulfapyridine was started even before the results of the cultures and smears had been reported. It was given in doses of 15 gr. every hour for four doses and subsequently 15 gr. every four hours. After the cultures had been reported, the drug was changed to sulfanilamide. The dosage was 20 gr. every four hours for twenty-four hours, then 15 gr. every four hours, and subsequently 10 gr. every four hours, until it was finally omitted on March 22.

The temperature came down to normal on March 18 and so remained throughout the subsequent convalescence. She was discharged in good condition on March 31, the seventeenth day after delivery.

The following white counts are of interest: March 16, 18,900; March 20, 21,000; March 21, 27,400; March 22, 29,900; March 23, 29,900; March 25, 26,400; March 26, 17,800; March 27, 14,900; March 28, 16,700; March 29, 12,600; March 30, 10,000. The sustained increased white count following the drop of the temperature to normal was probably due to the sulfanilamide.

Comment. This case illustrates the proper handling of certain cases of puerperal sepsis. The temperature of 99.6°F. twelve hours after delivery, with a rise to 102.6 eight hours later, suggests that the infection was present at the time of delivery. The administration of sulfapyridine before the cultures were reported and the shift to sulfanilamide afterward show the use of intelligent chemotherapy based on knowledge of the true etiologic factor. The uterus was left entirely alone.

*A series of selected case histories by members of the section will be published weekly. Comments and questions by subscribers are solicited and will be discussed by members of the section.

MEDICAL POSTGRADUATE EXTENSION COURSES

The following sessions, given by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health, the United States Public Health Service and the Federal Children's Bureau, have been arranged for the week beginning April 21:

BRISTOL SOUTH (Fall River Section)

Tuesday, April 23, at 4:30 p.m., at the Union Hospital, Fall River. Syphilis in Pregnancy and the Offspring. Instructor: Francis M. Thurmon. Howard P. Sawyer, *Chairman.*

HAMPDEN

Thursday, April 25, at 4:00 p.m., at the Academy of Medicine, Professional Building, 20 Maple Street, Springfield, and at 8:15 p.m., in the Outpatient Department of the Skinner Clinic, Holyoke Hospital, Holyoke. Complications in Obstetrics, Illustrated by Case Histories. Instructor: Roy J. Heffernan. George L. Schadt, *Chairman.*

HAMPSHIRE

Thursday, April 25, at 4:15 p.m., in the Nurses' Home of the Cooley Dickinson Hospital, Northampton. Syphilis in Pregnancy and the Offspring. Instructor: Francis M. Thurmon. Warren P. Cordes, *Chairman.*

MIDDLESEX SOUTH

Tuesday, April 23, at 4:30 p.m., at the Cambridge Hospital, 330 Mt. Auburn Street, Cambridge. Gonorrhea in the Female. Instructor: Sylvester B. Kelley. Dudley Merrill, *Chairman.*

NORFOLK SOUTH

Monday, April 22, at 8:30 p.m., at the Quincy City Hospital, Quincy. Cardiovascular Disease: Eleven important questions about heart disease and their answers. Instructor: Burton E. Hamilton. David L. Belding, *Chairman*.

PLYMOUTH

Tuesday, April 23, at 4:00 p.m., in the Nurses' Home of the Brockton Hospital, Brockton. Head and Spine Injuries. Instructor: Donald Munro. Walter H. Pulsifer, *Chairman*.

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BOWMAN, WILLIAM E., 1350 Massachusetts Avenue, North Adams.
Middlesex University School of Medicine, 1931.

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University of Lausanne Medical School, 1937.

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Middlesex University School of Medicine, 1928.

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Missouri College of Medicine and Science, 1927.

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Georgetown University School of Medicine, 1936.

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Tufts College Medical School, 1925.

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CUTLER, JOSEPH G., 236 Lafayette Street, Salem.
Johns Hopkins University School of Medicine, 1933.

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Tufts College Medical School, 1936.

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Middlesex University School of Medicine, 1931.

LOWD, HARRY M., JR., Salem Hospital, Salem.
University of Rochester School of Medicine, 1939.

MAIUZZO, ANTHONY M., 35 Broadway, Beverly.
Middlesex University School of Medicine, 1931.

PETT, MORRIS H., 54 Middle Street, Gloucester.
Middlesex University School of Medicine, 1930.

THOMAS, JOHN D., 38 Valley Road, Nahant.
College of Physicians and Surgeons, Boston, 1929.

J. Robert Shaughnessy, *Secretary*.

FRANKLIN DISTRICT

BOEH, LOUIS S., Conway.
Middlesex University School of Medicine, 1932.

Harry L. Craft, *Secretary*.

HAMPDEN DISTRICT

CLEVELAND, HAROLD F., 462 Belmont Avenue, Springfield.
Middlesex University School of Medicine, 1920.

FLEURY, EDGAR J., 332 Main Street, Holyoke.
Middlesex University School of Medicine, 1932.

GRACE, JAMES J., 91 Stockman Street, Springfield.
Middlesex University School of Medicine, 1934.

KOTARSKI, WILLIAM C., 700 Chestnut Street, Springfield.
Middlesex University School of Medicine, 1929.

SCHWARTZ, LEO, 760 Sumner Avenue, Springfield.
Middlesex University School of Medicine, 1934.

TATE, JOHN C., Westfield State Sanatorium, Westfield.
University of Tennessee College of Medicine, 1932.

Wayne C. Barnes, *Secretary.*

HAMPSHIRE DISTRICT

KING, MARION A., 58 Paradise Road, Northampton.
Boston University School of Medicine, 1938.

KOWALSKI, JOSEPH V., 67 South Street, Ware.
Middlesex University School of Medicine, 1933.

MICHELSON, HARRY H., State Hospital, Northampton.
University of Kiel, 1930.

PELSEN, HERMAN, Hampshire County Sanatorium, Haydenville.
Licentiate of Royal Colleges of Physicians and Surgeons, Edinburgh and Glasgow, Scotland, 1937.

Joseph D. Collins, *Secretary.*

MIDDLESEX EAST DISTRICT

BENSON, HARRY L., 312 Washington Street, Winchester.
Boston University School of Medicine, 1936.

COHEN, HARVEY H., 55 Pleasant Street, Woburn.
Middlesex University School of Medicine, 1932.

HEARNE, THOMAS M., 43 Stratford Road, Melrose.
Boston University School of Medicine, 1937.

MORELLI, DARIO, 17 Richardson Avenue, Wakefield.
Royal University of Naples, 1932.

Kenneth L. Maclachlan, *Secretary.*

MIDDLESEX NORTH DISTRICT

BLANEY, CYRIL A., Boston Road, Westford.
Boston University School of Medicine, 1902.

KAUFMAN, MANUEL, Tewksbury State Hospital and Infirmary, Tewksbury.
Tufts College Medical School, 1938.

SKRABUCHA, WILLIAM A., 310 Merrimack Street, Lowell.
Middlesex University School of Medicine, 1935.

SPRING, GEORGE V., Pleasant Street, East Pepperell.
Tufts College Medical School, 1937.

WARBURTON, NORMAN W., Goldsmith Street, Littleton Common.
Middlesex University School of Medicine, 1935.

Edward A. Payne, *Secretary.*

MIDDLESEX SOUTH DISTRICT

BALDWIN, GERTRUDE W., 988 Memorial Drive, Cambridge.
University of Pittsburgh School of Medicine, 1936.

BARBOUR, CHARLES M. JR., 1141 Walnut Street, Newton Highlands.
McGill University Faculty of Medicine, 1938.

BEER, PETER J. O., 234 Main Street, Waltham.
Ludwig-Maximilians-Universität, Munich, 1927.

CANNON, BRADFORD, 7 Healey Street, Cambridge.
Harvard Medical School, 1933.

CANZANELLO, VINCENT J., 385 Broadway, Everett.
Middlesex University School of Medicine, 1933.

COLANTINO, GEORGE J., 490 Highland Avenue, Malden.
Middlesex University School of Medicine, 1933.

CONROY, JOHN A., 183 Tremont Street, Newton.
Kansas City University of Physicians and Surgeons, 1933.

DRISCOLL, DANIEL T., 511 Pleasant Street, Malden.
Massachusetts College of Osteopathy, 1926.
Middlesex University School of Medicine, 1935.

DUCHIN, MAURICE S., 89 Magazine Street, Cambridge.
Chicago Medical School, 1929.

FINLEY, KNOX H., 27 South Crescent Circle, Brighton.
Yale University School of Medicine, 1930.

FISCHER, JOSEPH, 1942 Beacon Street, Brighton.
University of Vienna, 1915.

FOSTER, FRANK P., 31 Magnolia Avenue, Newton.
McGill University Faculty of Medicine, 1933.

FRIEDMAN, EMERICK, Metropolitan State Hospital, Waltham.
University of Buffalo School of Medicine, 1934.

GALL, EDWARD A., 77 Martin Street, Cambridge.
Tulane University of Louisiana School of Medicine, 1931.

GRINOLD, JOHN J., 225 Belmont Street, Belmont.
Middlesex University School of Medicine, 1932.

HAINES, GEORGE A., 641 Broadway, Everett.
Middlesex University School of Medicine, 1915.

KEVORKIAN, JOHN J., 104 Mt. Auburn Street, Watertown.
College of Physicians and Surgeons, Boston, 1934.

MACKILLOP, JOHN A., 381 Broadway, Cambridge.
Tufts College Medical School, 1938.

MORITZ, ALAN R., 19 Fenwick Road, Waban.
University of Nebraska College of Medicine, 1923.

NADEL, FREDERICK P., 55 Magazine Street, Cambridge.
Middlesex University School of Medicine, 1932.

OSGOOD, RUDOLF, 370 Common Street, Belmont.
Rush Medical College of the University of Chicago, 1932.

POLLAK, OTAKAR J., 124 Glenville Avenue, Allston.
Medical School of Masaryk University in Brno, 1930.

RAK, IAN P., 1 Oakland Street, Lexington.
University of Leipzig, 1933.

SELLMAN, PRISCILLA, 38 Beechcroft Road, Newton.
Boston University School of Medicine, 1936.

WATKINS, ARTHUR L., 68 Gray Street, Arlington.
Harvard Medical School, 1935.

Alexander A. Levi, *Secretary.*

NORFOLK DISTRICT

ALLENDORF, FRANCIS J., 118 Common Street, Walpole.
Middlesex University School of Medicine, 1933.

ALPERT, GEORGE R., 50 Verndale Street, Brookline.
University of California Medical School, 1936.

BALDWIN, ARTHUR D., 619 Washington Street, Wellesley.
Harvard Medical School, 1936.

BENDA, CLEMENS E., Wrentham State School, Wrentham.
University of Berlin, 1922.

BEREZIN, MARTIN A., Medfield State Hospital, Harding.
Boston University School of Medicine, 1937.

BONNER, HUGH J., 476 Centre Street, Jamaica Plain.
McGill University Faculty of Medicine, 1937.

CARMODY, ROBERT F., 1810 Beacon Street, Brookline.
Middlesex University School of Medicine, 1933.

CHAFETZ, MAX, 116 Norfolk Street, Dorchester.
Tufts College Medical School, 1931.

CIVEN, EVA, 1077 Blue Hill Avenue, Dorchester.
Middlesex University School of Medicine, 1925.

COMANDURAS, PETER, 25 Blue Hill Avenue, Roxbury.
Tufts College Medical School, 1933.

DOBELLE, MARTIN, 25 Littell Road, Brookline.
University of Ghent (Belgium) Faculty of Medicine, 1934.

FICICCHY, JOHN JR., 70 Arlington Street, Hyde Park.
Boston University School of Medicine, 1936.

FREEMAN, ROWLAND G. JR., Wilsondale Street, Dover.
Columbia University, College of Physicians and Surgeons, 1921.

GROSSMAN, SAMUEL, 32 Wenonah Street, Roxbury.
Kansas City University of Physicians and Surgeons, 1932.

GUDAS, PETER P., Boston State Hospital, Dorchester Centre.
Boston University School of Medicine, 1936.

HAND, LEO V., 93 Woodlawn Avenue, Wellesley Hills.
Temple University School of Medicine, 1933.

HINDMAN, DANIEL H., 221 Longwood Avenue, Boston (Roxbury).
Harvard Medical School, 1935.

HOCHMAN, GEORGE V., 20 Harding Street, Sharon.
Middlesex University School of Medicine, 1934.

KINSEY, DERA, 49 Beals Street, Brookline.
Baylor University College of Medicine, 1934.

LAPPIN, A. HENRY, 161 Harvard Street, Dorchester.
Tufts College Medical School, 1929.

LEADBETTER, WYLAND F., 16 Berkeley Court, Brookline.
Johns Hopkins University School of Medicine, 1932.

LEVISON, CARL, 4 Glenway Street, Dorchester.
Middlesex University School of Medicine, 1934.

LOWENBERG, BENJAMIN, 517 Washington Street, Dorchester.
Des Moines College of Osteopathy, 1930.
University of Lausanne Faculty of Medicine, 1939.

MEYERS, MARVIN T., 406 Centre Street, Jamaica Plain.
Kansas City University of Physicians and Surgeons, 1931.

MOORE, PAUL T., 259 Eliot Street, Milton.
Harvard Medical School, 1938.

MULLANEY, OWEN C., 50 Draper Street, Dorchester.
Boston University School of Medicine, 1937.

MUSHLIN, HARRY R., 1477 Beacon Street, Brookline.
Boston University School of Medicine, 1937.

PERONA, ATTILIO C., 12 Linden Street, Norwood.
Middlesex University School of Medicine, 1934.

PITTMAN, MERRY E., New England Hospital for Women and Children, Roxbury.
Rush Medical College of the University of Chicago, 1938.

SHRIBER, WILLIAM J., 27 Powellton Road, Dorchester.
University of Michigan Medical School, 1937.

SWEETSIR, FREDERICK N., 206 Riverway, Boston (Roxbury).
Tufts College Medical School, 1938.

TOUMEY, JAMES W. JR., Wampatuck Road, Dedham.
Columbia University, College of Physicians and Surgeons, 1926.

WEXLER, JACOB, 967 Blue Hill Avenue, Dorchester.
Middlesex University School of Medicine, 1933.

WILLGOOSE, DORATHEA M., 10 Noyes Street, Needham.
Philadelphia College of Osteopathy, 1932.
Middlesex University School of Medicine, 1935.

Frank S. Cruickshank, *Secretary.*

NORFOLK SOUTH DISTRICT

ELDER, BURTON F., Hingham.
Ohio State University College of Medicine, 1937.

FRANKMAN, WILLIAM, 736 Hancock Street, Wollaston.
St. Louis College of Physicians and Surgeons, 1921.

NOBILI, CONRAD, 14 Guild Street, Quincy.
Royal University of Rome Faculty of Medicine and Surgery, 1934.

PEARLSTEIN, MAX, 447 Washington Street, Braintree.
Tufts College Medical School, 1929.

Robert L. Cook, *Secretary.*

PLYMOUTH DISTRICT

FRITZ, LEWIS E., 34 Park Street, Stoughton.
Tufts College Medical School, 1926.

MATHEWS, MOLYNEAUX P., 28 Maple Avenue, Brockton.
Middlesex University School of Medicine, 1933.

POLLEN, DAVID A., 24 School Street, Middleboro.
Middlesex University School of Medicine, 1931.

Howard C. Reed, *Secretary.*

SUFFOLK DISTRICT

ALTSCHULE, MARK D., 74 Fenway, Boston.
Harvard Medical School, 1933.

CLARKE, SAMUEL T., 17 Pinckney Street, Boston.
Harvard Medical School, 1936.

CRANDON, JOHN H., Boston City Hospital, Boston.
Harvard Medical School, 1937.

DAVIS, BURNET M., 15 Phillips Street, Boston.
Harvard Medical School, 1937.

DONAGHY, GEORGE E., 270 Bay State Road, Boston.
Tufts College Medical School, 1934.

FISHGAL, MAURICE C., 394 West Broadway, South Boston.
Middlesex University School of Medicine, 1934.

GAHM, IRVIN G., Boston City Hospital, Boston.
Tufts College Medical School, 1939.

GATES, DONALD C., Gray, Maine.
Harvard Medical School, 1933.

GOLDMAN, MAX, Long Island Hospital, Boston.
Tufts College Medical School, 1936.

GOULD, DAVID M., Boston City Hospital, Boston.
Harvard Medical School, 1929.

HADLER, ARTHUR J., Long Island Hospital, Boston.
Harvard Medical School, 1935.

HAWKINS, RALPH L., 146 Marlboro Street, Boston.
Harvard Medical School, 1933.

HOXIE, THOMAS B., Boston City Hospital, Boston.
Tufts College Medical School, 1937.

LEVER, WALTER F., 22 West Cedar Street, Boston.
Universities of Heidelberg, Vienna, Zurich, Hamburg, Leipzig, 1934.

LEWIS, EMIL H., 107 Trenton Street, East Boston.
Boston University School of Medicine, 1936.

MALOOF, FREDERIC, 22 East Brookline Street, Boston.
Middlesex University School of Medicine, 1931.

MARVIN, FRANK W., 520 Commonwealth Avenue, Boston.
Harvard Medical School, 1916.

MOLLIVER, HENRY, 258 Washington Avenue, Chelsea.
Middlesex University School of Medicine, 1934.

NATHANSON, IRA T., 119 Peterboro Street, Boston.
Northwestern University Medical School, 1930.

NEWTON, AARON W., Boston City Hospital, Boston.
Tufts College Medical School, 1937.

SAPHIR, NELSON R., 616 Broadway, South Boston.
Washington University School of Medicine, 1936.

STEARNS, CARL, Long Island Hospital, Boston.
Tufts College Medical School, 1937.

THOMPSON, RICHARD H., 7 Exeter Street, Boston.
Harvard Medical School, 1934.

TWINAN, CLAIRE W., 86 Commonwealth Avenue, Boston.
State University of Iowa College of Medicine, 1934.

WARTHIN, THOMAS A., 112 Revere Street, Boston.
Harvard Medical School, 1934.

WISSING, EGON G., 750 Harrison Avenue, Boston.
University of Berlin, 1926.

WRIGHT, MARIAN L., 14 Buswell Street, Boston.
Boston University School of Medicine, 1936.

ZIEGLER, EDWIN E., United States Marine Hospital, Chelsea.
George Washington University Medical School, 1928.

ZOLL, PAUL M., 25 Peterboro Street, Boston.
Harvard Medical School, 1936.

Milton Henry Clifford, *Secretary.*

WORCESTER DISTRICT

ARNOLD, JESSE O., 2ND, 174 Park Avenue, Worcester.
Temple University School of Medicine, 1932.

BLOUIN, ALFRED R., 159 Hamilton Street, Southbridge.
Boston University School of Medicine, 1938.

FULDER, HANS, 10 Cottage Street, Worcester.
University of Lausanne, 1934.

GORDON, SYDNEY R., 208 Highland Street, Worcester.
Tufts College Medical School, 1937.

HINDS, CHARLES B. JR., 8 Paul Revere Road, Worcester.
Harvard Medical School, 1936.

KANT, OTTO, 10 Bruce Avenue, Shrewsbury.
Universities of Freiburg, Göttingen and Munich, 1923.

KAUFMAN, S. HARVARD, Worcester State Hospital, Worcester.
University of Wisconsin Medical School, 1936.

KEMBLE, ROBERT P., Worcester State Hospital, Worcester.
Jefferson Medical College, 1933.

LANKENNER, PETER A., 522 Grafton Street, Worcester.
Middlesex University School of Medicine, 1933.

MALAMUD, WILLIAM, Worcester State Hospital, Worcester.
McGill University Faculty of Medicine, 1921.

MELTZER, ADOLPH, 4 Amherst Street, Worcester.
Cornell University Medical College, 1934.

MEYERSOHN, FRANZ, 753 Pleasant Street, Worcester.
Friedrich-Wilhelms University, Berlin, 1915.

ROSENBLUM, HARRY A., Fiskdale.
Kansas City University of Physicians and Surgeons, 1932.

ROZANSKI, FRANK S., 554 Cambridge Street, Worcester.
Hahnemann Medical College and Hospital, 1937.

RUSSELL, FRANK H., 78 Burncoat Street, Worcester.
University of Tennessee College of Medicine, 1917.

SALOMON, ROBERT, 138 Elm Street, Worcester.
Universities of Frankfort, Heidelberg, Kiel, Freiburg, 1926.

SPIRA, BERTRAM, Worcester State Hospital, Worcester.
University of Illinois College of Medicine, 1935.

WALDMAN, JACOB E., 1131 Main Street, Leicester.
Tufts College Medical School, 1933.

George C. Tully, *Secretary.*

WORCESTER NORTH DISTRICT

COLBY, FRED B., 46 Oliver Street, Fitchburg.
University of Lausanne Medical School, 1937.

FAUST, PAUL J., Gardner State Hospital, East Gardner.
University of Colorado School of Medicine, 1929.

GROSSMAN, MYER J., 599 Main Street, Athol.
Middlesex University School of Medicine, 1933.

KILLELEA, EDWARD V., 40 Prichard Street, Fitchburg.
Baltimore Medical College, 1903.

SCHECHTMAN, HAROLD, 520 Main Street, Fitchburg.
Middlesex University School of Medicine, 1934.

TUCK, HERBERT A., Norcross Terrace, Fitchburg.
Tufts College Medical School, 1938.

Edward A. Adams, *Secretary.*

DEATHS

LORD — SIDNEY A. LORD, M.D., of Boston, died March 30. He was in his seventy-second year.

Dr. Lord received his degree from the Harvard Medical School in 1894 and specialized in neurology. He was a fellow of the Massachusetts Medical Society and the American Medical Association.

VAN GAASBEEK — GEORGE H. VAN GAASBEEK, M.D., of Springfield, died January 22. He was in his seventy-seventh year.

Dr. Van Gaasbeek received his degree from the Albany Medical College in 1893. He was a member of the Massachusetts Medical Society and the American Medical Association.

MISCELLANY

WHAT THE DOCTOR SHOULD KNOW

April is the month in which tuberculosis associations proclaim the importance of the early diagnosis of tuberculosis. Through various channels of publicity, the public is urged to take heed of the early symptoms. They are told also about the advantage of the tuberculin test and the x-ray as means of discovering tuberculosis even before symptoms appear. Physicians play their part by meeting the demand for more prompt and precise diagnosis. Dr. Henry C. Sweany, of the Research Laboratories of the City of Chicago Municipal Tuberculosis Sanatorium, who has contributed the following, sees clinical tuberculosis through the eyes of the pathologist familiar with end results. An understanding of what lies beneath the often obscure signals of approaching tuberculosis should be valuable to the practitioner whose field of battle is mostly in the sickroom.

• • •

After the tubercle bacillus was discovered, tuberculosis was soon found to be a generalized or systemic infection which only gradually becomes focalized in various organs as healing takes place. During the "generalization" phase there may be an ephemeral fever lasting from two to ten days, after which few symptoms occur until advanced disease appears. The majority of primary infections (about 80 per cent in America) take place in the lungs. The rate of infection varies widely in different countries, even in different communities, but is generally decreasing.

The first, or primary, infection in children occurs as varying sized patches of bronchopneumonia in the lung. From the local focus the bacilli follow the lymphatic vessels and form lesions in the various lymph nodes along the course of the lymphatics. The infection may finally reach the left subclavian vein whence it travels to the right side of the heart and becomes disseminated in the lungs. The bacilli many times pass through the pulmonary capillaries into the left side of the heart and from there to the general circulation to become deposited in all organs of the body.

All but an insignificant number of infections due to small inoculums heal, but where there has been heavy exposure the lesions heal in only about 75 per cent of the cases. The lesions that do not heal may slowly spread by growth or rupture into the bronchi or blood and lymph vessels. The infection may also spread from the lymph node lesions which may overflow and rupture. The bacilli may enter the blood stream, get into the general circulation, and cause a systemic dissemination. The average latent or quiescent period from the time of infection to the appearance of clinical disease has been found to be ten years.

Primary tubercles of adults, on the other hand, usually involve the lymph nodes less, have poorer capsules, and tend to localize more in the upper lung lobes. Therefore, the number of protracted primary "sequelar" lesions and exacerbations in the adults are fewer compared to those frequently found in the lymph nodes of children. For the same reason a more rapidly progressive pulmonary process is likely to occur in adults. In brief, when the adult type produces disease it proceeds rapidly and is confined largely to the lung parenchyma. The average latent period is usually about three years.

After the first infection there is an acquisition of allergy or hypersensitiveness of the body cells to tuberculin. This sensitization of the body cells is shown by the tuberculin skin reaction. A relative immunity also develops largely independent of the allergy, although the latter in moderate degree may contribute to the resistance to infection. In excessive degrees allergy may aggravate the infection. The effects of these changes in the basic nature of the host tend to cause a localization of the process in the body organs and tissues, most of which occurs in the lungs. This organ localization only develops gradually and is never complete except in cases that are healing.

The disease may continue as a "progressive primary lesion," an "exacerbation of a primary lesion," or be a much less frequent "new infection from without."

The majority of reinfection lesions are found along the subapical bronchi; the posterior upper quarters of both lungs are the sites of predilection in over 90 per cent of the early cases.

On the roentgenogram the lesions appear as small circumscribed or cloudy flecks a few millimeters in diameter.

The infection may spread to the other organs by the blood or lymphatic routes as it usually does during or after the primary infection. Direct implantations of bacilli cause laryngitis, enteritis and cystitis.

Following in the wake of the disease, non-specific "sequelar" lesions occur, including the distressing tracheobronchitis, bronchiectasis, bullous emphysema and, finally, heart failure due to fibrous obliteration of the pulmonary capillaries and arterioles.

Apart from the preceding conditions caused directly or indirectly by the tubercle bacillus there is the whole gamut of diseases that may be associated with tuberculosis as a concomitant or associated process. Skill is required to differentiate each one from tuberculosis.

The physician, therefore, seems to be just coming into his own in the diagnosis and treatment of tuberculosis. The medical man in the home has the best opportunity and is in the majority of cases the only one to get the disease under control early. This is a hopeful trend.

In Detroit, Douglas has observed that about 75 per cent of diagnoses of tuberculosis are made by the general practitioners. Pleyte's recent surveys in Wisconsin leave little doubt that the general practitioners can and should play an important role in case-finding. The contacts which made up 47.2 per cent of the group had fourteen times the infection rate as that for the state as a whole. The most important group of all was the group of cases submitted by the practitioners of the state who have been encouraged to send films to the Wisconsin Anti-Tuberculosis Association for consultation. This group of cases was made up of patients who had had a contact with an open case, were ill, or had been or were suspected of being ill. In this group the rate was forty times the average morbidity rate for the state. — Reprinted from *Tuberculosis Abstracts,* April, 1940.

NOTE

Dr. W. J. Merle Scott, associate professor of surgery, University of Rochester, and associate surgeon, Strong Memorial and Rochester Municipal hospitals, will be surgeon-in-chief *pro tempore,* Peter Bent Brigham Hospital, April 22 through 27. This custom of inviting physicians-in-chief and surgeons-in-chief *pro tempore* began when Dr. W. S. Thayer, of Johns Hopkins University School of Medicine, was invited to take charge of the medical wards from November 14 through 21, 1913. The visits permit a large exchange of thought between medical communities and are of great practical value to the house staff. Physicians and students are cordially invited to attend the ward rounds and teaching exercises.

NOTICES

PETER BENT BRIGHAM HOSPITAL

A joint medical and surgical clinic at the Peter Bent Brigham Hospital will be held on Wednesday, April 24, from 2 to 4 p.m. Drs. W. C. Quinby and E. A. Stead will speak on "Hematuria."

Physicians and students are cordially invited to attend.

HARVARD MEDICAL SOCIETY

A substitution of speakers has been made for the meeting of the Harvard Medical Society to be held in the amphitheater of the Peter Bent Brigham Hospital on Tuesday, April 23. Dr. Ravdin's illness prevents him from giving his lecture on "Some Recent Advances in Our Knowledge of the Biliary Tract," as originally announced

in the April 11 issue of the *Journal*. The revised program is as follows:

Presentation of cases.

Some Problems in the Proper Emptying of Hollow Viscera. Dr. W. J. Merle Scott, of Rochester, New York.

JOINT MEETING OF THE SUFFOLK DISTRICT MEDICAL SOCIETY AND THE BOSTON MEDICAL LIBRARY

A joint meeting of the Suffolk District Medical Society and the Boston Medical Library will be held on Wednesday evening, April 24, at 8:15, at the Boston Medical Library, 8 Fenway, Boston.

PROGRAM

Official reports of the Society for 1938.

Election of officers.

Atom Smashing as a New Tool for Medical Research (with demonstration). Dr. J. J. Livingood. Discussion will be opened by Drs. Shields Warren, Francis T. Hunter and Saul Hertz.

BOSTON DOCTORS' SYMPHONY ORCHESTRA

The first concert of the Boston Doctors' Symphony Orchestra, Alexander Thiede, conductor, will be held at 8:15 on Sunday evening, May 5, at Jordan Hall. Tickets are priced at one dollar, and the proceeds will be given to a medical charity. The ticket committee is composed of Dr. Welman B. Christie, chairman, 15 Bay State Road, Boston, Dr. Julius Loman, 1284 Beacon Street, Brookline, and Dr. Robert G. Vance, 262 Beacon Street, Boston.

HENRY JACKSON LECTURE

The Henry Jackson Lecture for 1940 offered by the New England Heart Association will be given by Dr. Harrison S. Martland, chief medical examiner of Essex County, New Jersey, and professor of forensic medicine, New York University College of Medicine. His subject will be "Sudden Deaths with Reference to Their Prevention." The lecture will be held at the Boston Medical Library on Friday, April 26, at 8:15 p.m.

Interested physicians and medical students are invited to attend.

MASSACHUSETTS DEPARTMENT OF CIVIL SERVICE AND REGISTRATION

PUBLIC WELFARE PHYSICIAN (MALE), DEPARTMENT OF PUBLIC WELFARE

Director of State Civil Service, Ulysses J. Lupien, has announced that a competitive examination is to be held on May 11 in order to find eligibles for appointment to the position of Public Welfare Physician, Department of Public Welfare. The entrance salary is $3780 a year; the maximum is $4500 a year.

The entrance requirements are as follows: applicants must be registered physicians under the State Board of Registration in Medicine, and must have at least five years' experience in the practice of medicine, at least one year of which shall have been spent as an intern in a hospital approved for internship by the American Medical Association.

The substitution is as follows: satisfactory full-time experience in a medical administrative capacity in a hospital, public-health organization, department of public health or department of public welfare within the past five years may be substituted year for year for the years of experience required in the practice of medicine, except for the year of internship. The substitution of education is: education may be substituted for experience, year for year of graduate study in a school of public health.

The subjects and weights of the examination are as follows: training and experience, 2; practical questions, 3; total, 5. Applicants must obtain a grade of 70 per cent in each subject in order to become eligible. The last date for filing applications is Saturday, April 27.

NEW ENGLAND ROENTGEN RAY SOCIETY

The next meeting of the New England Roentgen Ray Society will be held in the main amphitheater of the Children's Hospital on Friday, April 26, at 8:00 p.m.

PROGRAM

Craniolacunia: A report of 54 cases. Dr. E. C. Vogt.

Genitourinary Diagnosis and Treatment in Infants and Children: Persistent pyuria, kidney embryoma and retroperitoneal neuroblastoma. Drs. G. M. Wyatt and W. E. Ladd.

Tumors in Early Life. Dr. Sidney Farber.

Dinner at the Harvard Club will be served at 6:30 p.m.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING SUNDAY, APRIL 21

TUESDAY, APRIL 23

*9–10 a.m. Ovarian Tumors. Dr. J. T. Smith. Joseph H. Pratt Diagnostic Hospital.

12:30 p.m. An Experiment in the Delivery of Medical Care. Dr. Channing Frothingham. Community Nursing Council of Boston. Young Women's Christian Association, 140 Clarendon Street, Boston.

*8:15 p.m. Harvard Medical Society. Amphitheater of the Peter Bent Brigham Hospital (Shattuck Street entrance).

WEDNESDAY, APRIL 24

*9–10 a.m. Hospital case presentation. Dr. S. J. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*2–4 p.m. Hematuria. Drs. W. C. Quinby and E. A. Stead. Peter Bent Brigham Hospital.

*8 p.m. Massachusetts Dental Society. Georgian Room, Hotel Statler.

8:15 p.m. Joint meeting of the Suffolk District Medical Society and the Boston Medical Library. 8 Fenway, Boston.

THURSDAY, APRIL 25

*9–10 a.m. Off the Main Road in Diabetes. Dr. J. J. Schloss. Joseph H. Pratt Diagnostic Hospital.

FRIDAY, APRIL 26

*9–10 a.m. Small-Bowel Obstruction. Dr. L. S. McKittrick. Joseph H. Pratt Diagnostic Hospital.

8 p.m. The Clinical Interpretation of Bacteremia. Dr. Chester S. Keefer. Sir William Osler Honorary Society of the Tufts College Medical School. Beth Israel Hospital auditorium.

8 p.m. New England Roentgen Ray Society. Children's Hospital main amphitheater.

*8:15 p.m. Sudden Deaths with Reference to Their Prevention. Dr. Harrison S. Martland. Henry Jackson Lecture. Boston Medical Library, 8 Fenway.

SATURDAY, APRIL 27

*9–10 a.m. Hospital case presentation. Dr. Thannhauser. Joseph H. Pratt Diagnostic Hospital.

*Open to the medical profession.

APRIL 18 and 19 — Quincy City Hospital. Page 654, issue of April 11.

APRIL 24–26 — Scientific Session. Academy of Physical Medicine. Page 654, issue of April 11.

APRIL 25 — New England Society of Psychiatry. Page 654, issue of April 11.

MAY 5 — Boston Doctors' Symphony Orchestra concert. Notice above.

MAY 9 — Pentucket Association of Physicians. 8:30 p.m., Hotel Bartlett, Haverhill.

MAY 10–18 — American Scientific Congress. Page 1043, issue of December 28.

MAY 13 — United States Pharmacopoeial Convention. Page 202, issue of February 1.

MAY 21–22 — Massachusetts Medical Society. Annual meeting, Boston.

JUNE 4–7 — American Association of Industrial Physicians and Surgeons. Page 654, issue of April 11.

JUNE 7–8 — American Heart Association. Page 469, issue of March 14.

JUNE 7–10 — American Board of Obstetrics and Gynecology. Page 608, issue of April 4.

JUNE 8 and 10 — American Board of Ophthalmology. Page 719, issue of November 2.

JUNE 10–14 — American Medical Association. Annual meeting, New York City.

JUNE 10–14 — American Physicians' Art Association. Page 332, issue of February 22.

JUNE 23–25 — Maine Medical Association. Annual meeting. Rangeley Lakes.

OCTOBER 8–11 — American Public Health Association. Page 655, issue of April 11.

OCTOBER 21 — American Board of Internal Medicine, Inc. Page 369, issue of February 29.

District Medical Societies

ESSEX SOUTH

MAY 8 — Annual meeting. Salem Country Club, Peabody.

FRANKLIN

MAY 14 — Franklin County Hospital, Greenfield.

HAMPSHIRE

MAY 8, at 11:30 a.m. at the Cooley Dickinson Hospital, Northampton.

MIDDLESEX EAST

MAY 15, at 12:15 p.m. at the Unicorn Country Club, Stoneham.

MIDDLESEX NORTH

APRIL 24.

JULY 31.

OCTOBER 30.

NORFOLK SOUTH

MAY 2.

PLYMOUTH

APRIL 18 — State Farm.

MAY 16 — Lakeville State Sanatorium, Middleboro.

SUFFOLK

APRIL 24 — Annual meeting in conjunction with the Boston Medical Library. Election of officers. Page 697.

MAY 2 — Censors' meeting. Page 244, issue of February 8.

WORCESTER

MAY 8 — Worcester Country Club. Dinner at 6:30 p.m. followed by a business and scientific meeting.

BOOKS RECEIVED FOR REVIEW

Displacement of the Calcified Pineal Body in Roentgen Pictures as an Aid in Diagnosing Intracranial Tumours: An anthropometrical-statistical analysis. Bengt Lilja. Acta Radiologica Supplementum XXXVII. 183 pp. Stockholm: P. A. Norstedt & Söner, 1939. Swed. Cr. 10.

King Gustaf V's Stockholm Jubilee Clinic for Radiotherapy and Research in Cancer: A description. Gösta Forssell, Elis Berven, Olle Reuterwall and Rolf Sievert. Acta Radiologica Supplementum XXXVIII. 80 pp. Stockholm: P. A. Norstedt & Söner, 1939. Swed. Cr. 8.

Cancer in Childhood: And a discussion of certain benign tumors. Edited by Harold W. Dargeon. 114 pp. St. Louis: C. V. Mosby Co., 1940. $3.00.

Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord: A concise introduction to the principles of localization of diseases and injuries of the nervous system. Robert Bing. Translated and edited by Webb Haymaker. Eleventh edition. 292 pp. St. Louis: C. V. Mosby Co., 1940. $5.00.

Frontier Doctor. Urling C. Coe. 264 pp. New York: The Macmillan Co., 1940. $2.50.

Treatment of War Wounds and Fractures: With special reference to the closed method as used in the war in Spain. J. Trueta. 146 pp. New York: Paul B. Hoeber, Inc., 1940. $2.50.

Psychological Studies in Dementia Praecox. Isabelle Kendig and Winifred V. Richmond. 211 pp. Ann Arbor: Edwards Brothers, Inc., 1940. 50c.

Fundamentals of Dentistry in Medicine and Public Health. John O. McCall. 161 pp. New York: The Macmillan Co., 1938. $2.75.

Artificial Pneumothorax: Its practical application in the treatment of pulmonary tuberculosis. Contributions by Saranac Lake physicians to the studies of the Trudeau Foundation. Edited by Edward N. Packard, John N. Hayes and Sidney F. Blanchet. 300 pp. Philadelphia: Lea & Febiger, 1940. $4.00.

Fractures and Other Bone and Joint Injuries. R. Watson-Jones. 723 pp. Baltimore: Williams & Wilkins Co., 1940. $13.50.

BOOK REVIEWS

The Rockefeller Foundation: Annual report, 1938. 515 pp. New York: The Rockefeller Foundation, 1939.

This annual report of the Rockefeller Foundation covers, as usual, the work of the International Health Division, reports of the divisions on medical sciences, natural sciences, social sciences and the humanities and the work in China. In addition, there are the reports of the secretary, the president and the treasurer. There is an excellent index, and a number of illustrations. Such a volume cannot be easily reviewed for it covers so wide a field.

To those who are interested in what the Rockefeller Foundation is accomplishing and how its large grants of money are being allocated each year, this book is widely recommended. It is interesting to note that the appropriation for medical sciences to the China Medical Board was nearly four million dollars. One of the major activities of the Foundation has been in relation to psychiatry, neurology and related subjects. In 1938, it helped to develop departments of neurology and psychiatry in five medical schools, with the expenditure of over two million dollars. In looking to the future, the president points out that fields of medical research which might be expanded include chemotherapy, dermatology, pharmacology, legal medicine, industrial medicine, dentistry, public health and the diseases of advancing years.

Handbook of Orthopaedic Surgery. Alfred R. Shands, Jr. In collaboration with Richard B. Raney. Second edition. 567 pp. St. Louis: C. V. Mosby Co., 1940. $4.25.

The first edition of this book has found a definite place in the teaching of orthopedic surgery to medical students, and is valuable to those in general practice because the essentials are briefly stated, and the subjects well covered. The new edition is smaller than the first, chiefly because the paper is thinner, rather than because of changes in material. The book is divided into twenty-four chapters, corresponding to the number of hours ordinarily devoted to lectures on the subject in the average medical school.

The illustrations are made up of line drawings, there being no direct reproductions of x-ray films or pathologic specimens. This makes for simplicity without affecting the value of the book for teaching purposes. A valuable part of both the first and second editions, especially for medical students, is the current bibliography, rather selective, corresponding to each chapter and confined to the English language. This gives the student a chance for further reading without making too many demands in the searching for collateral titles.